Synthetic studies towards a tandem Pummer-Thianazarov cyclisation and a photomediated asymmetric synthesis of cuparene

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A Photomediated Asymmetric Synthesis of (–)-Cuparene

A thesis presented by

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This thesis is dedicated to my mother and father, Farida and Yakub Patel.

Abstract

The challenge of establishing adjacent quaternary centres within a cyclopentane ring has made the cuparene and herbertene class of sesquiterpenoids popular synthetic targets. However, the additional challenge of controlling the absolute stereochemistry at the sterically hindered quaternary stereocentre has meant that far fewer of these approaches can or have been rendered asymmetric. This report describes a fundamentally new approach to the asymmetric synthesis of cuparene based on a concept of "asymmetric photochemistry", a potentially powerful yet virtually unexplored area in modern asymmetric synthesis.

The introductory chapter is a review of the asymmetric synthesis of the sesquiterpenes cuparene, cuparenone, herbertene, herbertendiol and mastigophorenes A and B. This is followed by a summary of the photochemistry of amines.

A total synthesis of both racemic and enantiomerically pure (–)-cuparene is described in chapter 2. The generation of the benzylic quaternary centre via a photomediated cyclisation of both racemic and chiral (aminobutyl)styrenes followed by microwave-assisted Cope elimination is discussed. Results on the photochemical cyclisation of a variety of C_2-symmetric and non-C_2-symmetric chiral (aminobutyl)styrene derivatives is also reported.

The experimental procedures are presented in chapter 3.

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Abbreviations

DET	diethyl tartrate
t-Bu	*tert*-butyl
LDA	lithium diisopropylamide
HMPA	hexamethylphosphoramide
THF	tetrahydrofuran
DIBALH	di-*iso*-butylaluminium hydride
Ph	phenyl
tol	tolyl
Py	pyridine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
m-CPBA	*meta*-chloroperbenzoic acid
BuLi	butyllithium
DMSO	dimethylsulfoxide
TBHP	*tert*-butylhydroperoxide
DMF	*N, N*-dimethylformamide
DMAP	dimethylaminopyridine
TMSCl	chlorotrimethylsilane
PDC	pyridinium dichromate
o-DCB	1, 2-dichlorobenzene
TBAF	tetrabutylammonium fluoride
NMO	*N*-methylmorpholine-*N*-oxide
DDQ	2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone
TLC	thin layer chromatography
DCC	N, N'-dicyclohexylcarbodiimide

TPAP	tetrapropylammonium perruthenate
HRP	horseradish peroxidase
equiv.	equivalent
h	hour
ee	enantiomeric excess
DCNB	dicyanobenzene
hν	irradiation
THP	tetrahydropyran
rt	room temperature
CSA	camphor sulfonic acid
KHMDS	potassium hexamethyldisilazane
LiHMDS	lithium hexamethyldisilazane
n-butyl	normal-butyl
Triton B	benzyltrimethylammonium hydroxide
c	concentration
°C	degrees centigrade
w/w	weight for weight
DHP	3, 4-dihydro-2H-pyran
PPTS	pyridinium-*p*-toluenesulfonate
PPSE	trimethylsilyl polyphosphate
NMR	nuclear magnetic resonance
M	molar
Min	minute
μW	microwave

Nuclear Magnetic Resonance

δ	chemical shift
br	broad
s	singlet
d	doublet
t	triplet
dd	double doublet
dt	double triplet
m	multiplet
ppm	parts per million
J	coupling constant
NOE	nuclear overhauser effect

IR Spectroscopy

w	weak
m	medium
s	strong
br	broad

Mass Spectrometry

m/z	mass/charge
EI	electron ionisation
FAB	fast atom bombardment
CI	chemical ionisation
HRMS	high resolution mass spectrometry

Chapter 1

Background/Introduction

The development of methodology for the enantioselective construction of carbon centres with four non-hydrogen substituents, that is, quaternary carbon centres, is a challenging and important goal in organic synthesis.[1] The construction of benzylic quaternary centres is of great consequence, since it is a common substructure in a number of biologically significant compounds. Prominent amongst these are an expanding family of sesquiterpenes, the cuparenes and herbertanes. These are characterised by the presence of adjacent quaternary carbon atoms on a cyclopentane ring, but differ in the position of methyl substitution on the aromatic ring. Some of these compounds, particularly those with oxygen functionalities, show a wide spectrum of biological activity, including potent antifungal, neurotrophic and antilipid peroxidation activity (Figure 1).[2]

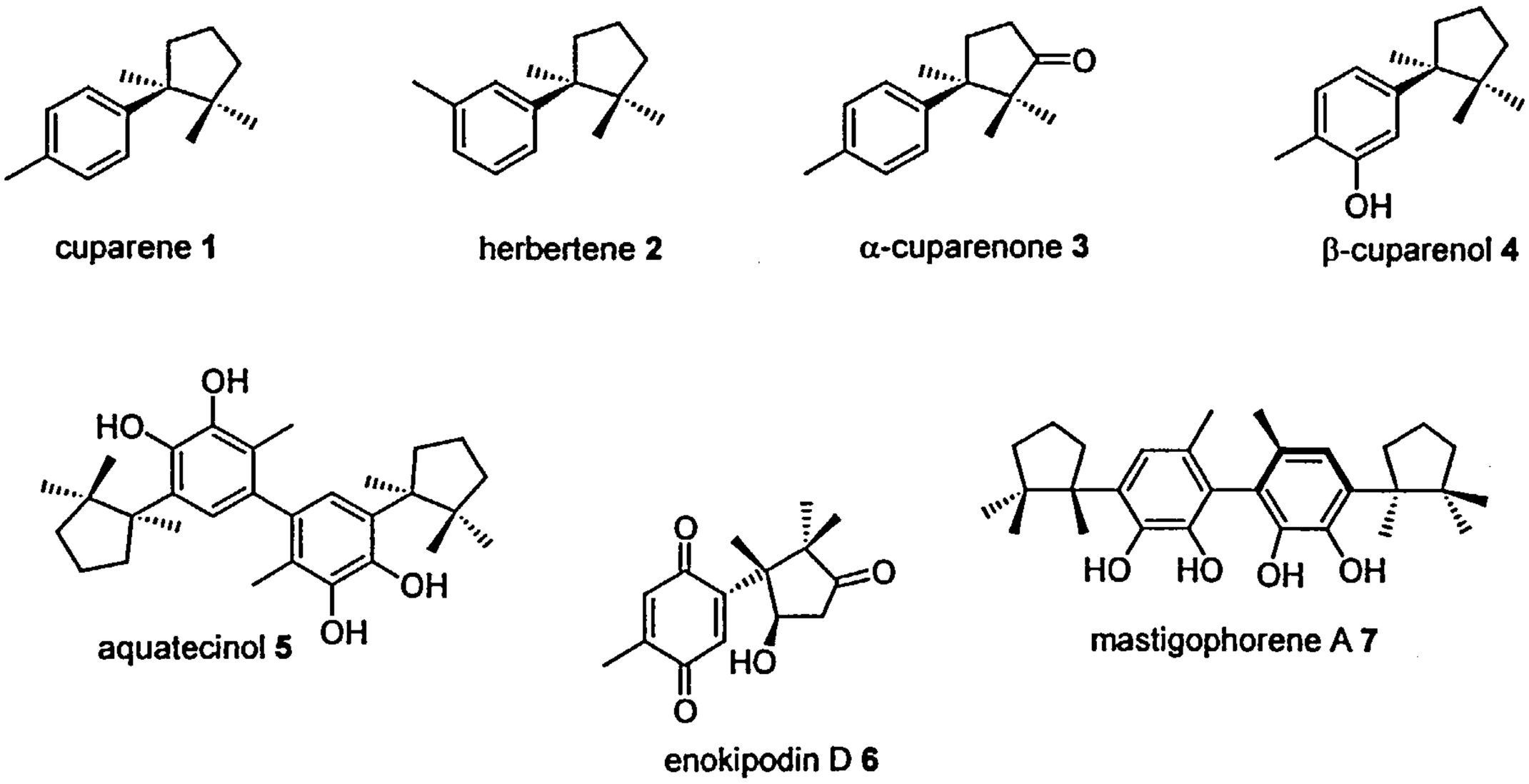


Figure 1

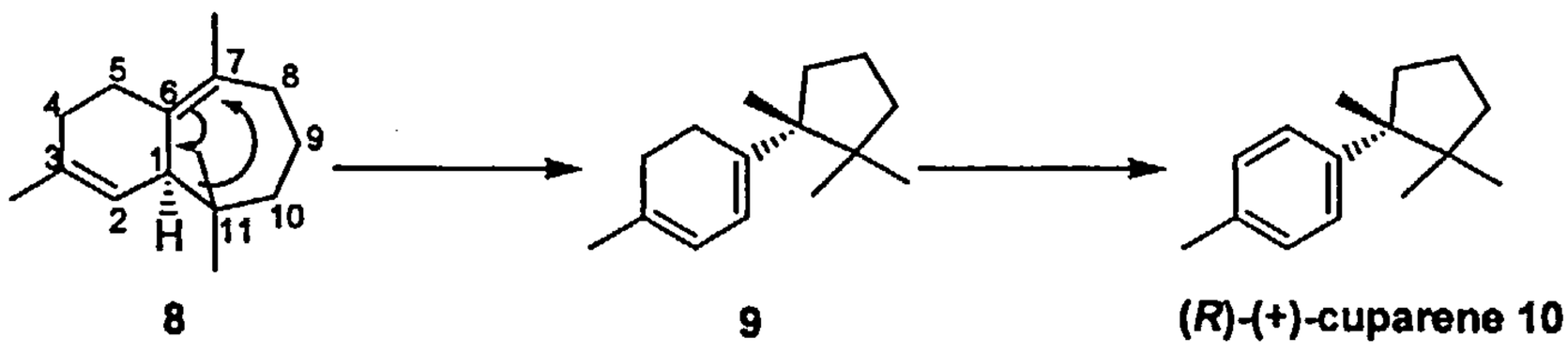
The challenge of establishing this key structural feature, a hindered quaternary stereocentre on a five membered ring, has made these compounds popular synthetic

targets. This is attested by the appearance of more than sixty publications,[3] addressing the various aspects of establishing two adjacent quaternary carbon atoms.[4] However the additional challenge of controlling the absolute stereochemistry at the sterically congested quaternary stereocentre has meant that far fewer of these approaches can or have been rendered asymmetric.

1.1 Synthetic approaches to enantioenriched cuparene

(+)-Cuparene was first isolated from the heartwood of conifers *Chamaecyparis thyoides* by Enzell and Erdman in 1958.[5] Matsuo *et al.* reported the isolation of the (–)-enantiomer from the liverwort *Bazzania pompeana* in 1975.[6] To date there have been four pathways developed for the synthesis of cuparene in enantiopure form.[7]

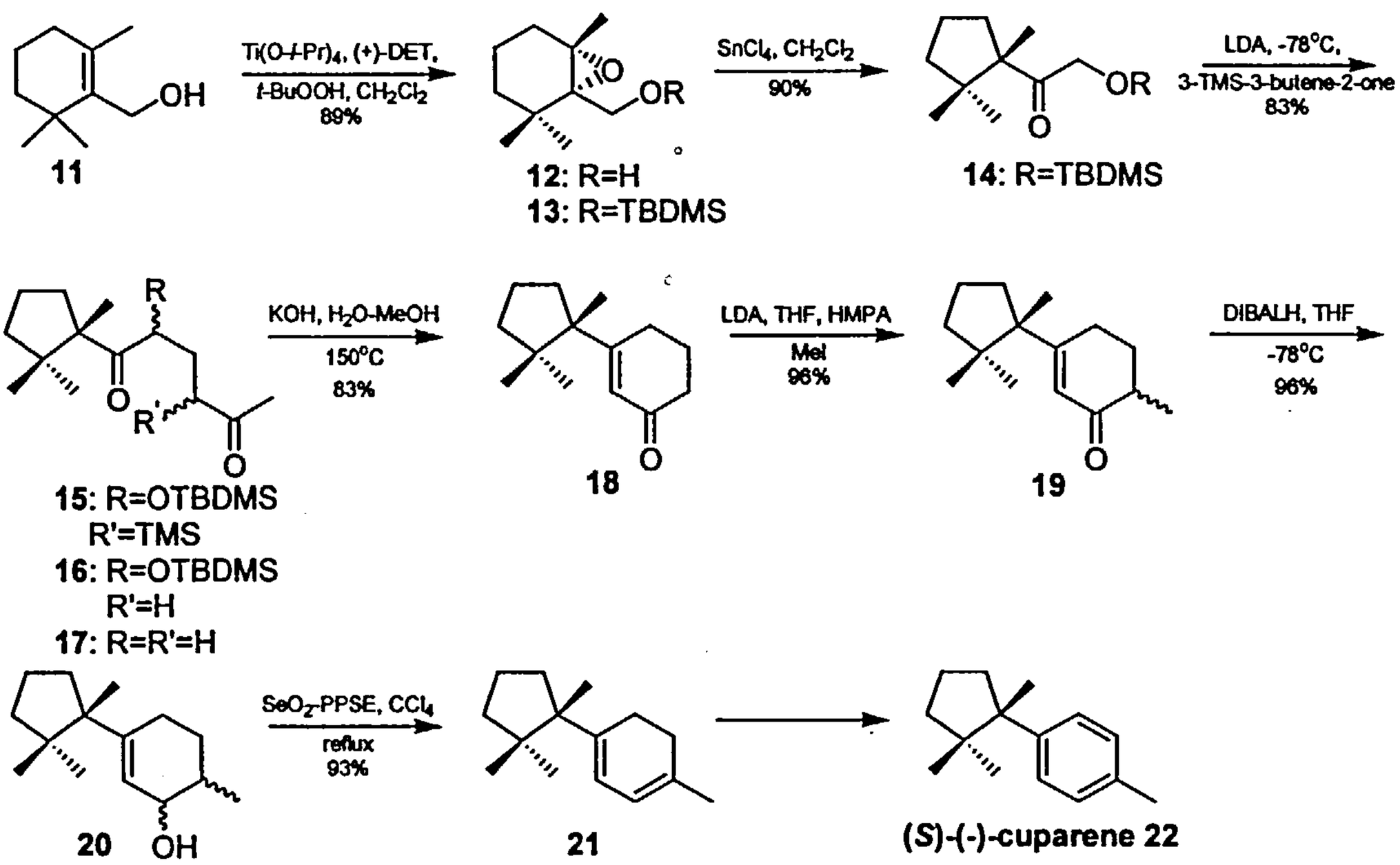
The first synthesis by Dev and co-workers produced enantiomerically enriched cuparene from a one-step thermal rearrangement of (+)-β-himachalene **8**.[7a] (+)-Cuparene resulting from the pyrolysis of **8** had an $[\alpha]_D$ +12.47 and was isolated in ~30%. The mechanism is thought to be partly concerted and proposed to proceed via the migration of C_{11} to C_7 from the β-face to afford (*R*)-(+)-cuparene **10** in approximately 20% optical purity (Scheme 1).



8 **9** **(*R*)-(+)-cuparene 10**

Scheme 1

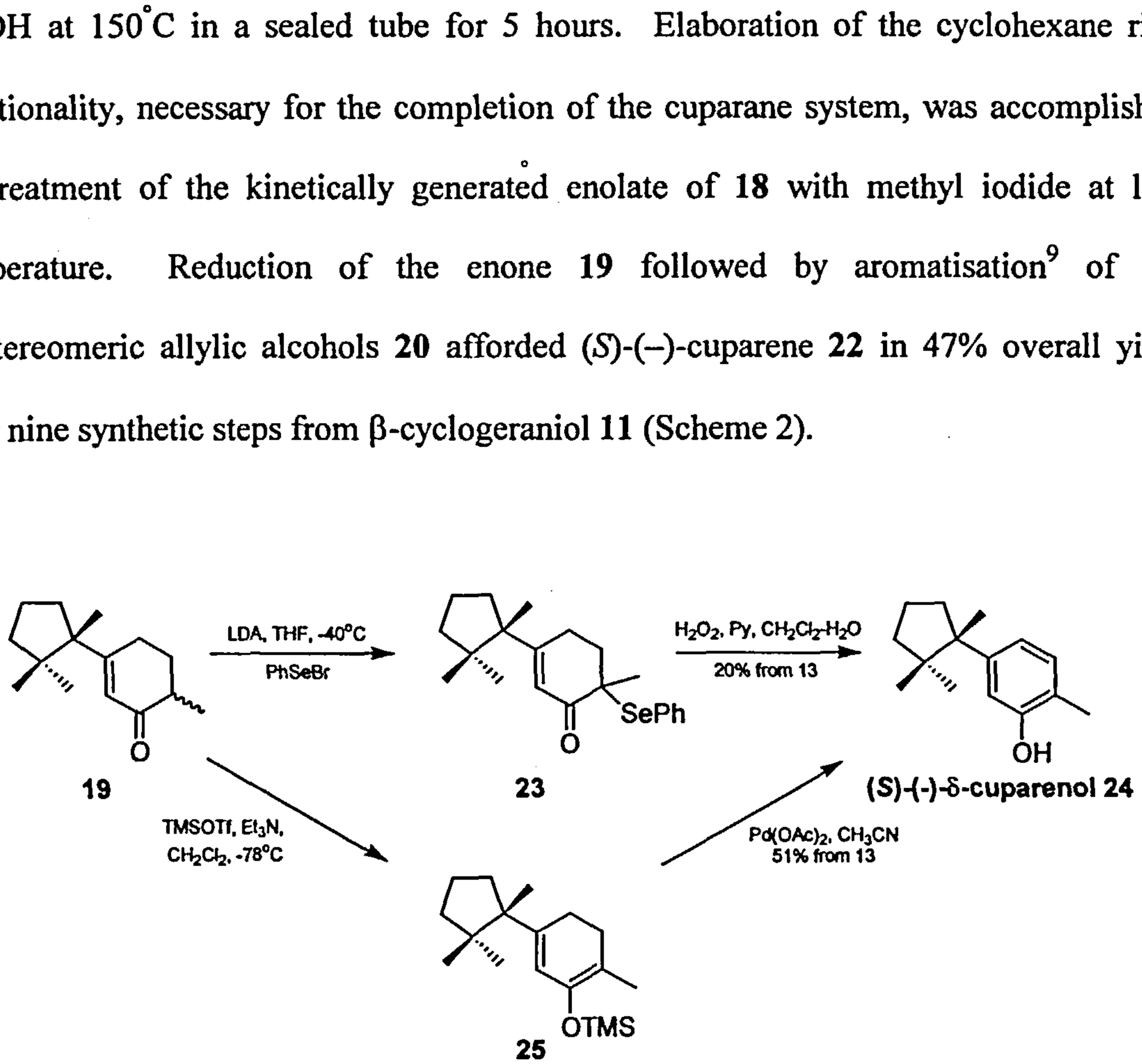
Some time later Abad et al. reported on a new enantioselective synthesis of cuparane type sesquiterpenoids (*S*)-(–)-cuparene **22** and (*S*)-(–)-δ-cuparenol **24**.[7b] These representative members were synthesised from β-cyclogeraniol **11** in 47% and 27% overall yields respectively. A Katsuki-Sharpless asymmetric epoxidation, pinacol rearrangement and classical Robinson annulation methodology were used as key synthetic steps (Scheme 2).



Scheme 2

Epoxidation of **11** with the Sharpless L-(+)-DET reagent gave the epoxy alcohol **12** in good yield and high enantiomeric purity (98% ee). Conversion of the hydroxy group of **12** to the corresponding *tert*-butyldimethylsilyl ether **13** followed by Lewis acid-promoted pinacol rearrangement afforded enantiomerically pure (–)-(*S*)-**14** as the chiral synthon. Build-up of the aromatic ring was accomplished by Michael addition of the

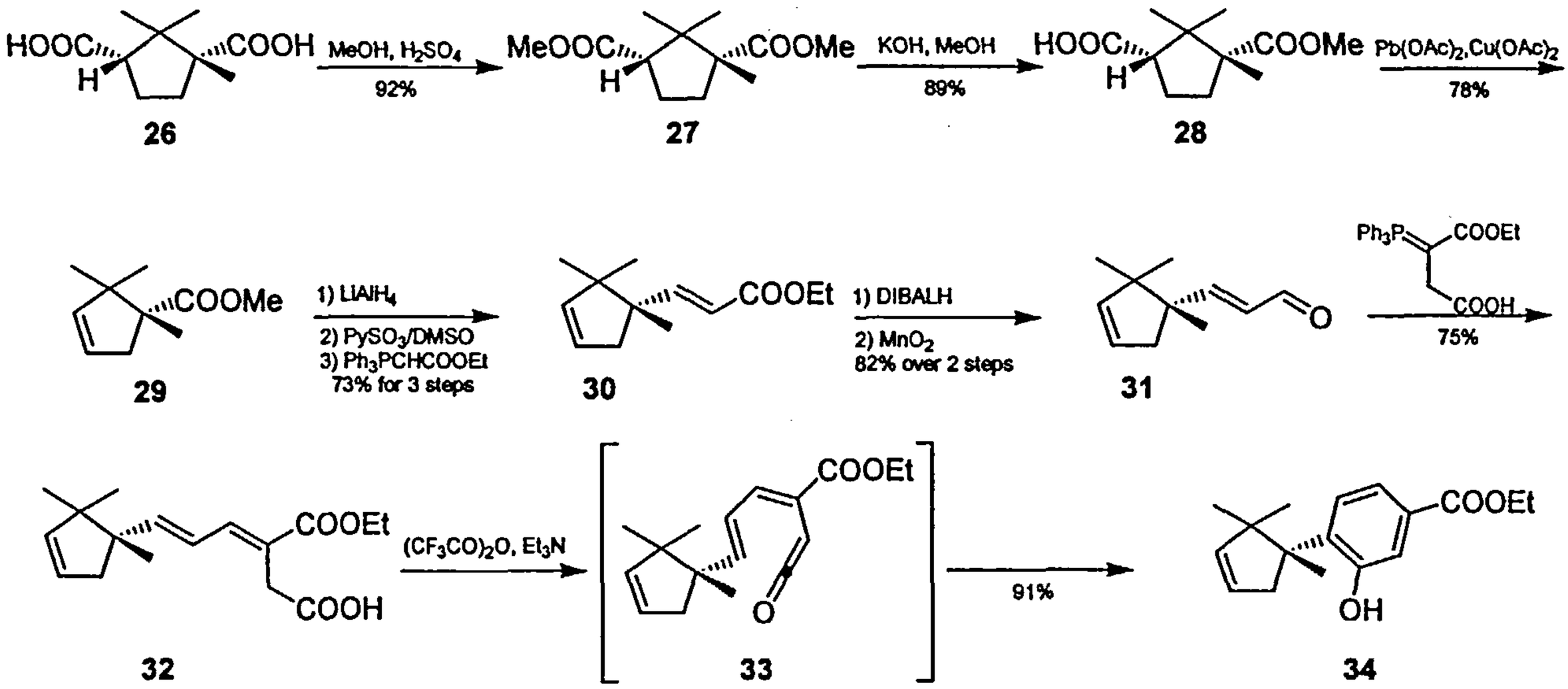
lithium enolate of **14** with 3-trimethylsilyl-3-butene-2-one which gave a mixture of adducts **15** and desilylated compound **16**.[8] Treatment of the crude mixture with 1% KOH in methanol cleaved the trimethyl-silyl moiety affording compound **16** as a diastereomeric mixture. Attempts to complete the annulation process via an intramolecular aldol reaction were unsuccessful under a variety of conditions. However, after removal of the trimethylsilyloxy group using SmI_2 in THF and MeOH clean conversion to **18** could be effected by treatment of **17** with 4% aqueous KOH in MeOH at 150°C in a sealed tube for 5 hours. Elaboration of the cyclohexane ring functionality, necessary for the completion of the cuparane system, was accomplished by treatment of the kinetically generated enolate of **18** with methyl iodide at low temperature. Reduction of the enone **19** followed by aromatisation[9] of the diastereomeric allylic alcohols **20** afforded (*S*)-(–)-cuparene **22** in 47% overall yield over nine synthetic steps from β-cyclogeraniol **11** (Scheme 2).



Scheme 3

The synthesis of (*S*)-(–)-δ-cuparenol **24** was achieved in two ways. Reaction of the lithium enolate of enone **19** with benzeneselenenyl bromide gave the selenated ketone **23**. Subsequent oxidation using hydrogen peroxide in aqueous methylene chloride and pyridine afforded the target compound **24** in overall good yield. More conveniently, conversion of **19** to the silyl enol ether **25**, followed by oxidation with palladium(II) acetate in acetonitrile also afforded (*S*)-(–)-δ-cuparenol **24** in 27% yield over nine synthetic steps from **11** (Scheme 3).

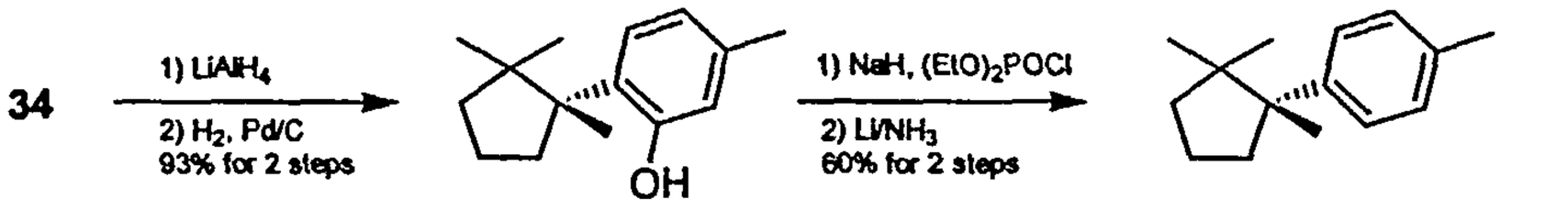
A few years later, Serra et al.[7c] reported on a new synthesis of (+)-3-hydroxycuparene **35** and (+)-cuparene **10**, again constructing the aromatic ring starting from an enantiopure cyclopentane building block. The chiral acid **32** required to test the already developed benzoannulation reaction[10,11] was prepared in nine steps from commercially available (+)-camphoric acid **26**.



Scheme 4

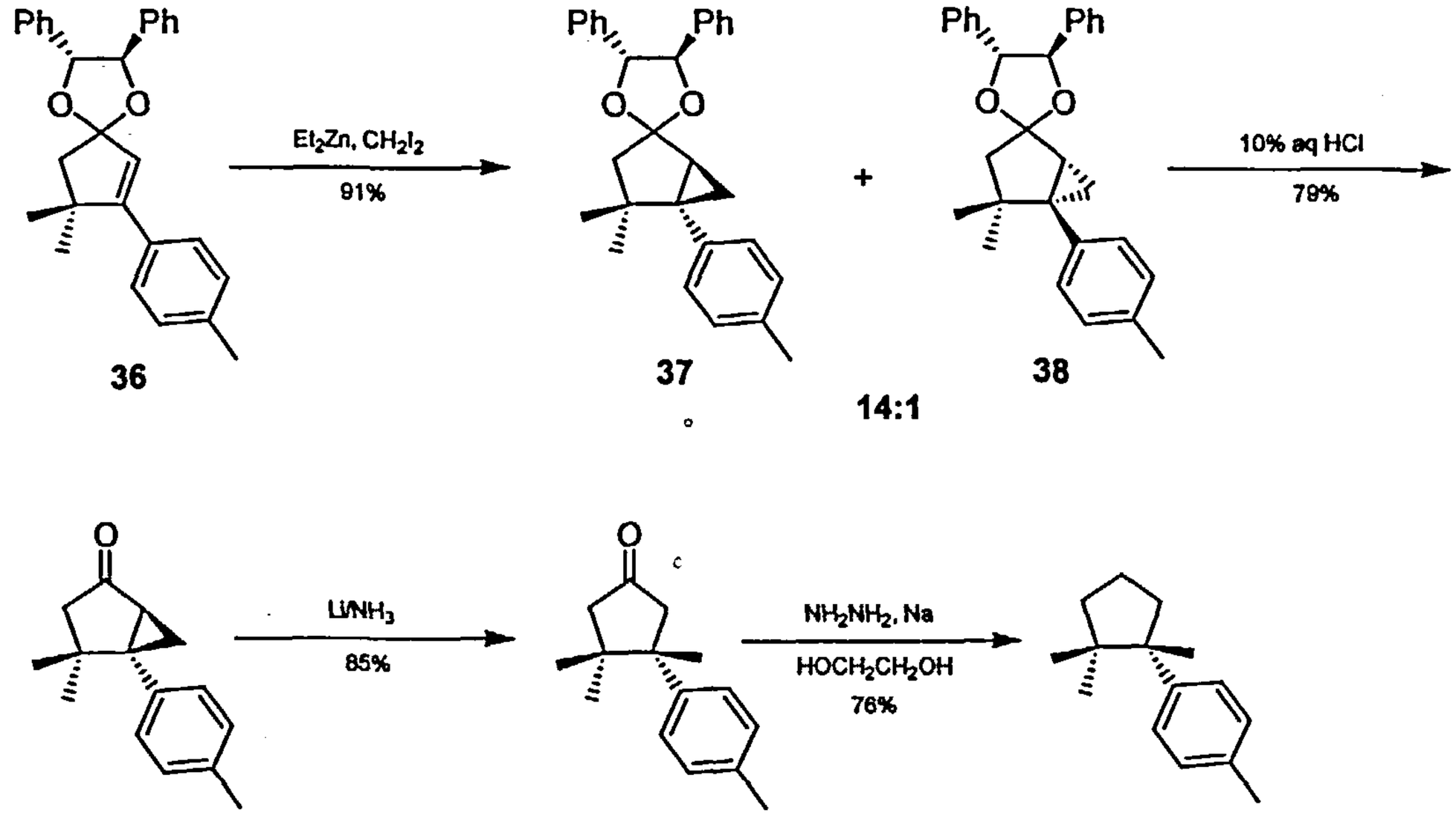
The dimethyl ester of **26** was regioselectively hydrolysed using methanolic KOH to give acid **28**.[12] Oxidative decarboxylation affected using lead tetraacetate and copper acetate[13], followed by reduction, $PySO_3$ oxidation[14] and homologation with (carbethoxymethylene)triphenylphosphonium betaine gave ester **30**. Compound **30** was then converted into the aldehyde **31** via DIBALH reduction and MnO_2 oxidation. Wittig reaction with triphenyl(α-carbethoxy-β-carboxyethyl)phosphonium betaine lead to acid **32**, which upon activation underwent a 1,6-electrocyclisation involving divinylketene intermediate **33** to afford phenol derivative **34** (Scheme 4).[10,11]

Reduction of the ester group using $LiAlH_4$ followed by hydrogenolysis of the benzylic alcohol afforded enantiopure (+)-3-hydroxycuparene **35**. Deoxygenation[15] of (+)-3-hydroxycuparene **35** by reduction of the diethyl phosphate ester gave (*R*)-(+)-cuparene **10**. (+)-3-Hydroxycuparene **35** was first detected in the liverwort of *Herbertus subdentatus*, while the (–)-enantiomer was isolated only recently from *Lejeunea aquatica* during a chemosystematic study (Scheme 5).[16]



Scheme 5

A completely different approach to the synthesis of (*S*)-(–)-β-cuparenone **40** and (*S*)-(–)-cuparene **22** has been reported by Mash *et al.*[7d] His strategy involves enantioselective construction of the quaternary centre starting from a framework which contains the aromatic ring.[17]



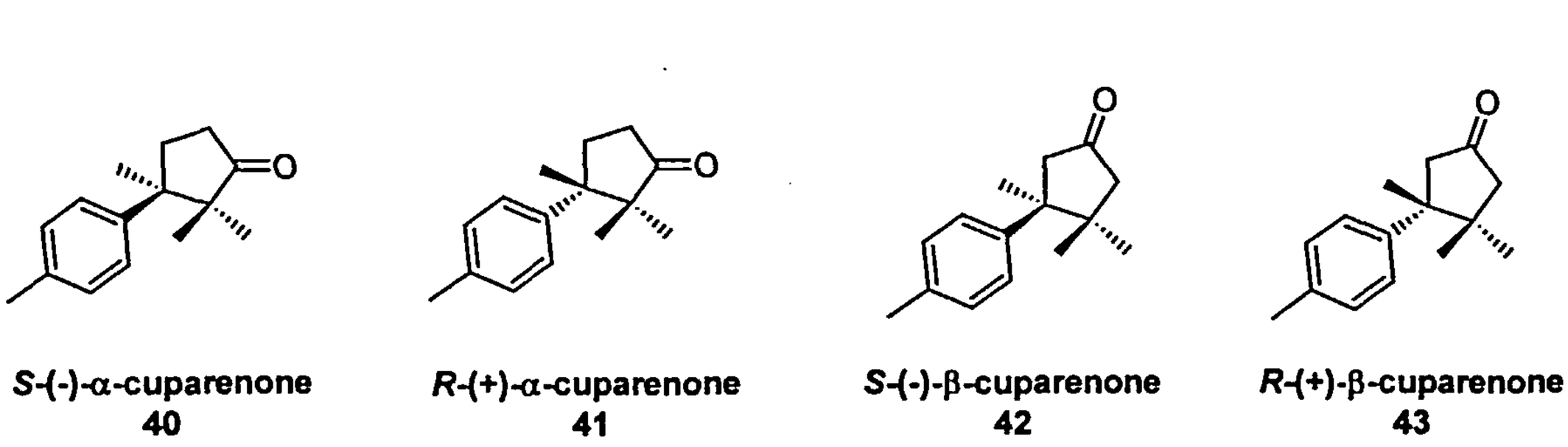
Scheme 6

Diastereoselective cyclopropanation reaction on ketal **36,** using Denmark's protocol[18] gave an inseparable 14:1 mixture of cyclopropane ketals **37** and **38.** Hydrolysis of this mixture using 10% aqueous HCl in methanol gave the enantiomerically enriched cyclopropyl ketone **39** in ~ 87% ee. This underwent a regiospecific cyclopropane ring cleavage[17,19] with lithium in liquid ammonia to furnish (*S*)-(-)-β-cuparenone **42** in 51%, over 4 steps. Finally treatment of the latter under modified Huang-Minlon Wolff-Kishner reduction[20] conditions gave (*S*)-(–)-cuparene **22** in 76% yield and $[\alpha]_D^{20}$=-58.3 (*c* 0.3, $CHCl_3$) (Scheme 6).

1.2 Synthetic approaches to enantioenriched α and β-cuparenone

Elaboration of the C5 cyclopentane and C6 aromatic rings has led to the synthesis of different members of the cuparane family, the bicyclic sequiterpenoids α-cuparenone and β-cuparenone.[21] More than 15 publications addressing the various approaches of establishing the two contiguous quaternary centres, that provide optically active natural products have appeared.

Chetty and Dev isolated and characterised the (+)-enantiomers, *R*-(+)-α-cuparenone **41** and *R*-(+)-β-cuparenone **43** in 1964 from the essential oils of the *Mayur Pankhi* tree.[22] The (–)-enantiomers, *S*-(–)-α-cuparenone **40** and *S*-(–)-β-cuparenone **42** were later isolated from the liverwort *Mannia fragrans*.[23]



S-(-)-α-cuparenone **40**

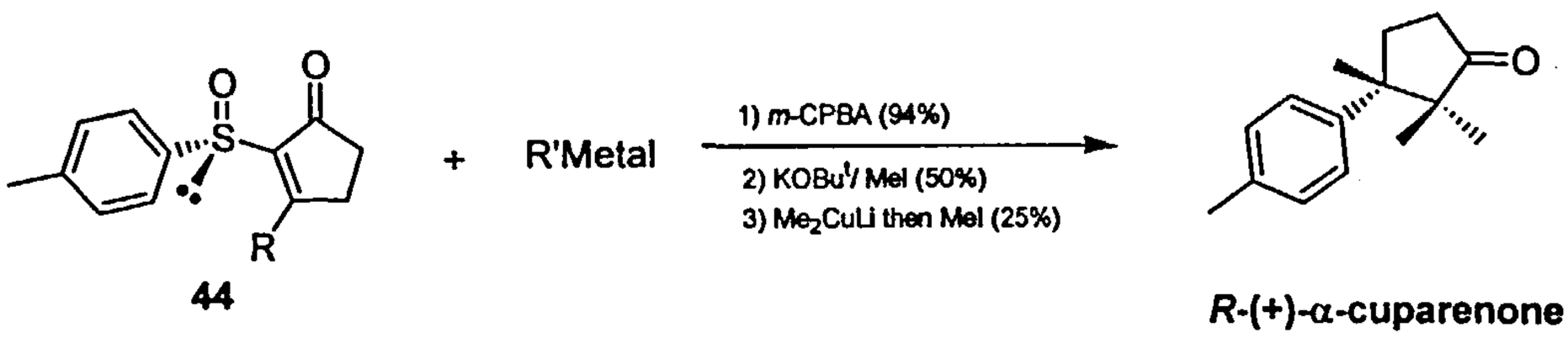
R-(+)-α-cuparenone **41**

S-(-)-β-cuparenone **42**

R-(+)-β-cuparenone **43**

Figure 2

Stereocontrolled formation of α-cuparenones **40** and **41** was first reported by Posner.[24] His methodology employed an asymmetric conjugate addition of ditolylcopperlithium reagent to enantiomerically pure 3-methyl-2-(*p*-tolylsulfinyl)cyclopentanone **44** (Scheme 7).[25]



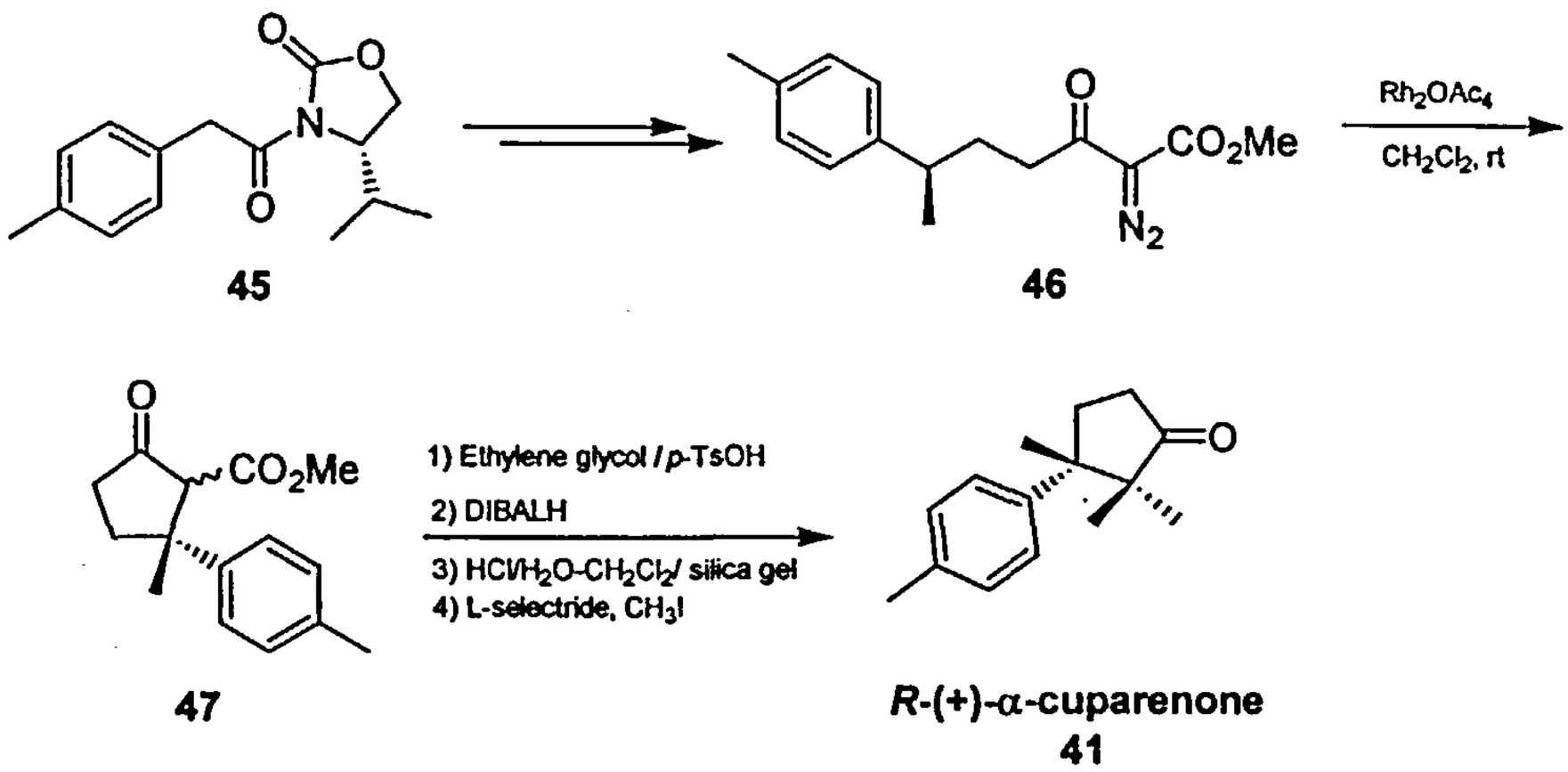
44

***R*-(+)-α-cuparenone**
41

Scheme 7

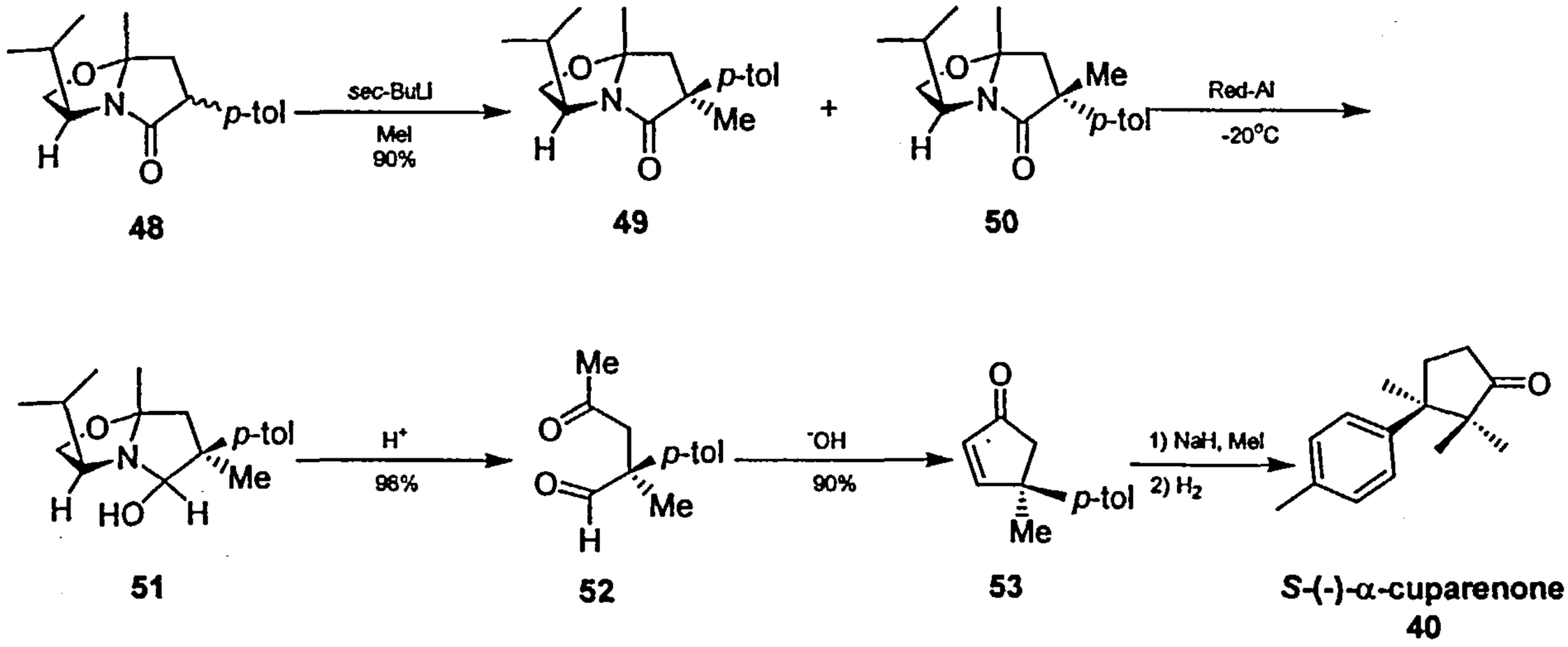
Transfer of chirality from the sulfoxide sulfur atom to the β-carbon, during the asymmetric conjugate addition step, followed by C-methylation[26] and reductive removal of sulfur produced **41** in 71% enantiomeric purity. Addition of a methyl grignard to 3-tolyl-cyclopentenone sulfoxide of type **44**, ie. reversal of the sequence of addition, leads to the opposite enantiomer **40** (Scheme 7).

α-Diazo-β-keto esters, readily prepared by Weiler's method[27] followed by diazo transfer[28], are known to undergo intramolecular C-H insertion reactions in a metal-catalysed system.[29] Taber has shown that exposure of α-diazo-β-keto ester **46**, prepared from oxazolidinone **45**, to a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2 can lead to an enantioselective ring closure to afford a diastereomeric mixture of cyclopentanones **47**.[30] Presumably, the transition state for 1,5-H transfer is preferred over that for 1,6-H transfer, leading to the 5 rather than the 6 membered ring. Furthermore, the C-H insertion step proceeded with complete retention of configuration at the optically pure ternary centre. Modification of a three step Marx procedure[31] converted the ester functionality in **47** to the geminally dialkylated cyclopentanone **41** in 96% optical purity (Scheme 8).



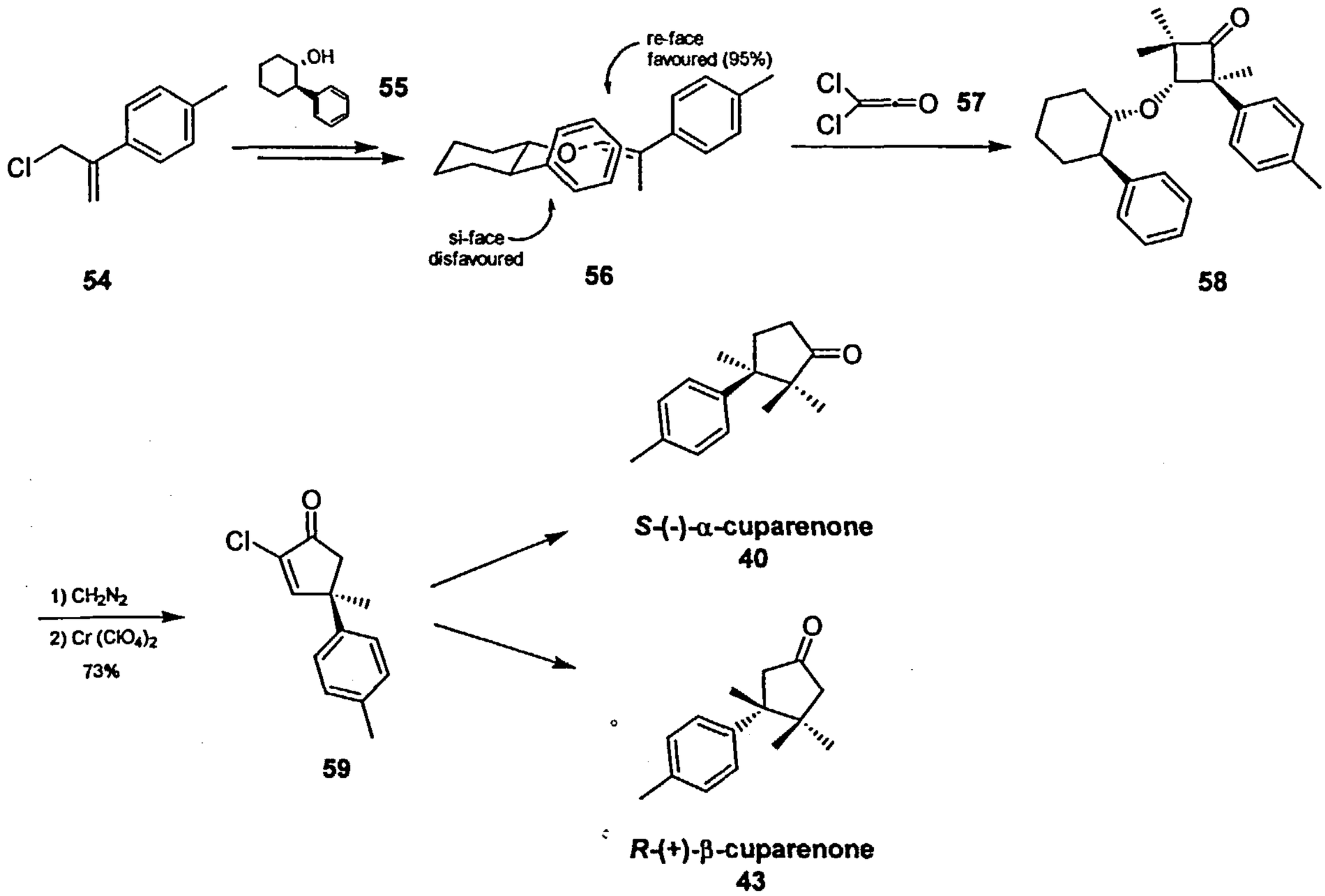
Scheme 8

Chiral bicyclic lactam **48**, produced as a 1:1 mixture of endo/exo diastereomers from the cyclocondensation of 2-*p*-tolyl-4-oxopentanoic acid and (*S*)-valinol, has been employed in the synthesis of **40**.[32] Treatment of **48** with *sec*-butyllithium and methyl iodide afforded compounds **49** and **50** as a 93:7 separable mixture, probably via the generation of a single lithium enolate from metalation at the α-position, that is predominantly alkylated from the less hindered endo face. Reduction of lactam **49** followed by hydrolysis with tetrabutylammonium dihydrogen phosphate gave keto aldehyde **52**. Aldol cyclisation, followed by the introduction of the geminal dimethyl group[33] and removal of the double bond moiety produced **40** in ~98% ee (Scheme 9).



Scheme 9

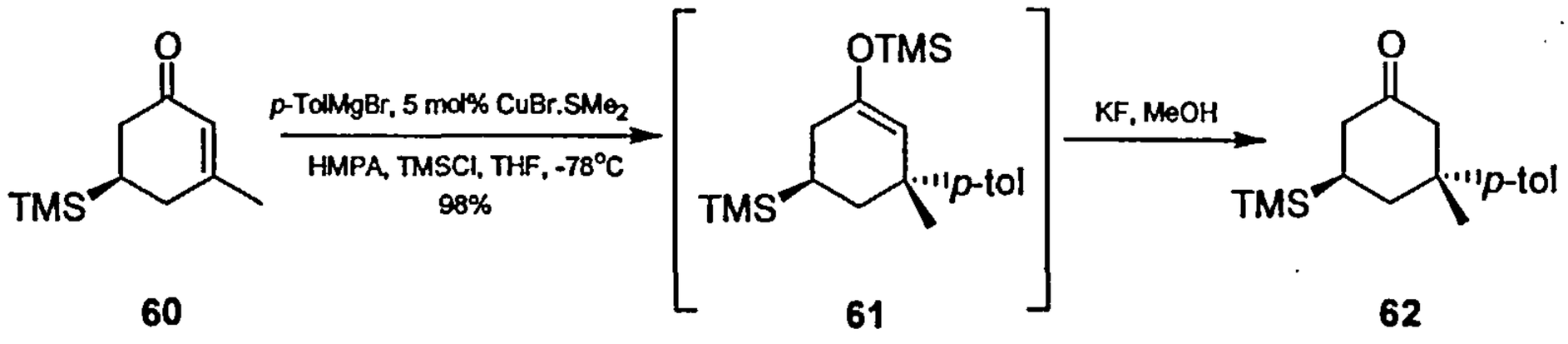
The use of (*1R, 2S*)-(+)-2-phenylcyclohexanol **55** as a chiral auxiliary offered π-face diastereoselection during a [2+2] cycloaddition reaction between chiral enol ether **56** and dichloroketene **57**.[34] Chiral enol ether **56**, prepared from allylic chloride **54**, entered into reaction with dichloroketene through a favourable π-face discriminating transition state. For steric reasons **56** adopts a nearly *s*-trans conformation, effectively bearing the C_α-Re face of **56** to attack by the ketene, whilst placing the C_α-Si in a sterically shielded environment. This establishes the key benzylic stereocentre with minimum induction 95:5 in favour of cyclobutanone **58** (Scheme 10).



Scheme 10

Purification followed by ring expansion[35] with diazomethane and removal of the auxiliary furnished versatile α-chloroenone **59**, which was converted to both **40** and **43** via α, α-dimethylation and β, β-dimethylation[36] respectively (Scheme 10).

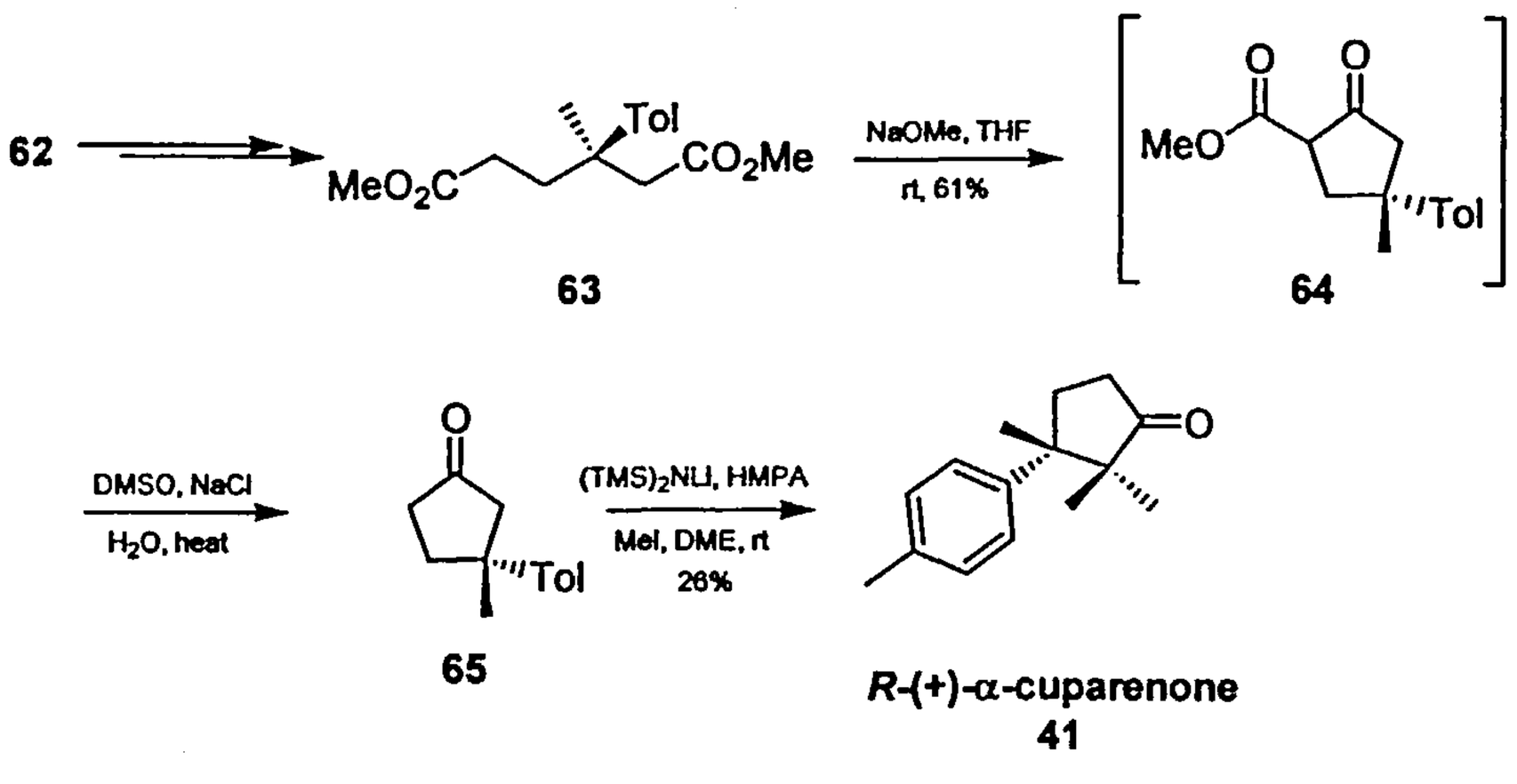
Conjugate addition of Grignard reagents to 3-substituted 5-trimethylsilyl-2-cyclohexanones **60** have been applied towards the synthesis of quaternary centres, resulting in high optical purity.[37] Asaoka and coworkers demonstrated the utility of this strategy in their synthesis of *R*-(+)-α-cuparenone **41**. 1,4-Addition of *p*-TolMgBr to optically pure enone **60** in the presence of 5 mol% CuBr-SMe_2, followed by subsequent KF hydrolysis of the product silyl enol ether **61** afforded the 1,4 adduct **62** in 98% yield (Scheme 11).



60 61 62

Scheme 11

Silicon-directed regioselective Baeyer-Villiger oxidation,[38] ring-opening of the resulting lactone and subsequent conversion to the diester gave compound **63**. Dieckmann cyclisation of **63** in the presence of NaOMe in THF gave a β-ketoester which upon treatment with NaCl in wet DMSO afforded 3,3-disubstituted cyclopentanone **65**. Neighbouring group directed dimethylation[39] furnished **41** in good optical purity. Rao and co-workers have published a formal synthesis of **40** and **43** starting from the diacid of **63**.[40] The quaternary stereocentre was produced from resolution of the racemic acid using brucine followed by a two-carbon homologation.

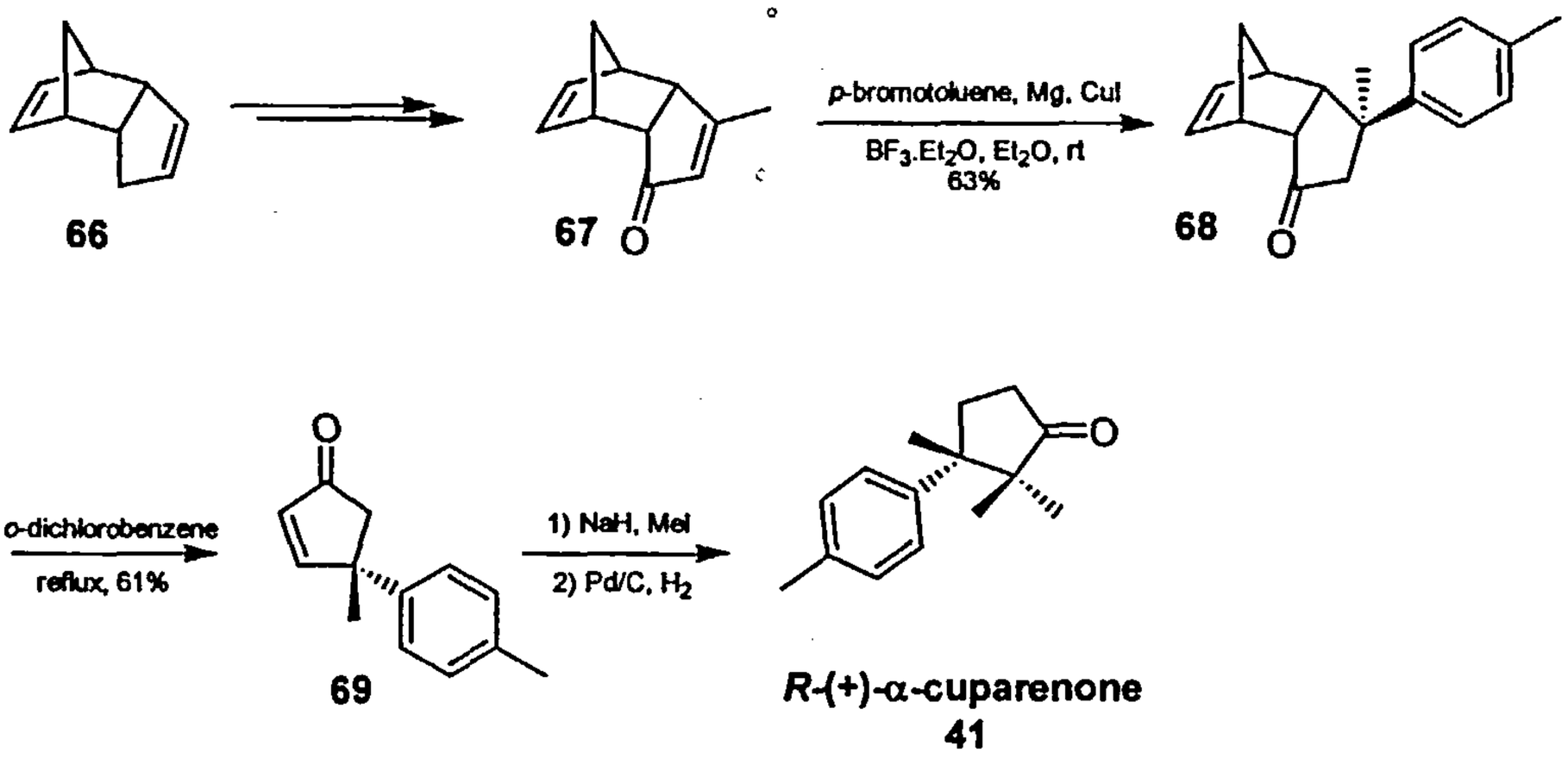


63 64 65

R-(+)-α-cuparenone
41

Scheme 12

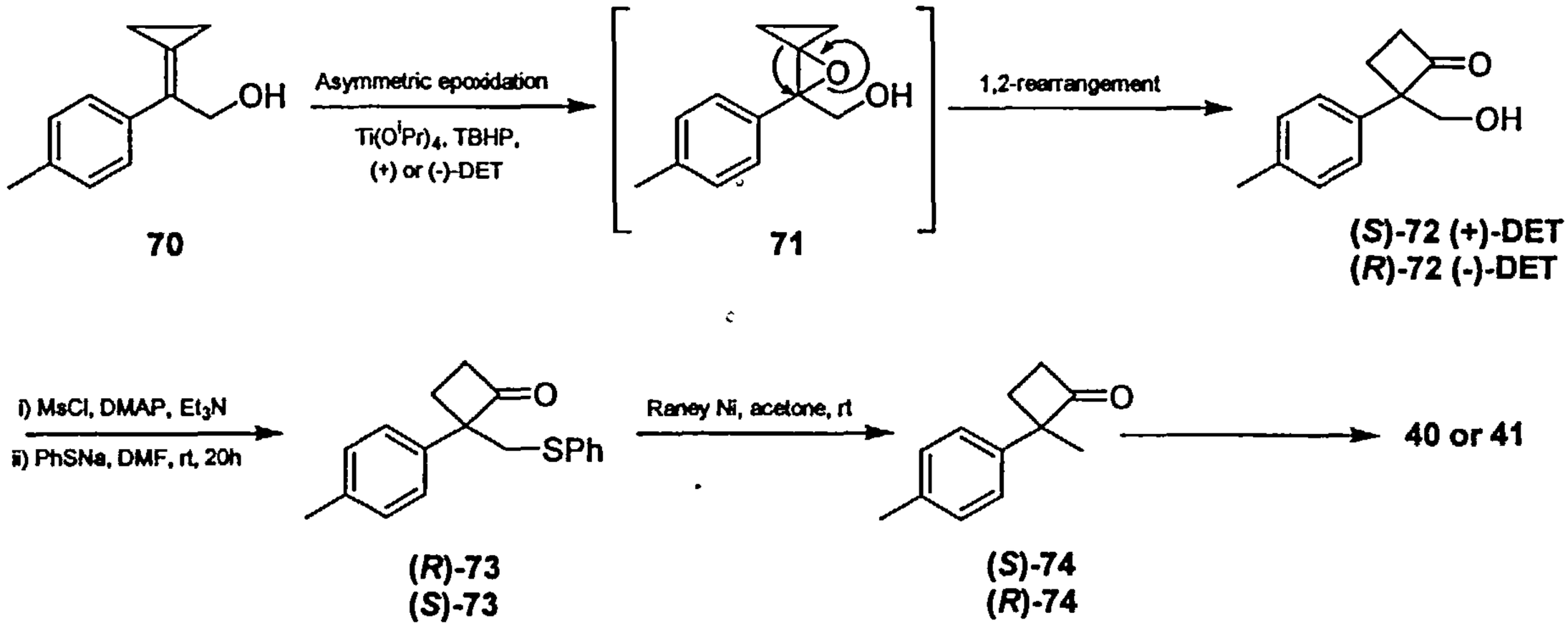
Takano and coworkers[41] developed an enantioconvergent route to **41** from chiral dicyclopentadienone **67**, synthesised by an already established procedure from racemic dicyclopentadiene **66**. The role of **67** is to act as a stereoselective synthetic equivalent of cyclopentadienone. It undergoes conjugate addition reactions with *p*-tolylmagnesium bromide to the convex face, in the presence of copper (I) iodide and boron trifluoride-etherate.[42] This results in a 1,4 adduct **68**, which upon reflux in 1,2-dichlorobenzene undergoes a retro-Diels-Alder reaction to form the enantiopure, substituted cyclopentanone **69**,[32] constituting a formal synthesis of **41** (Scheme 13).



Scheme 13

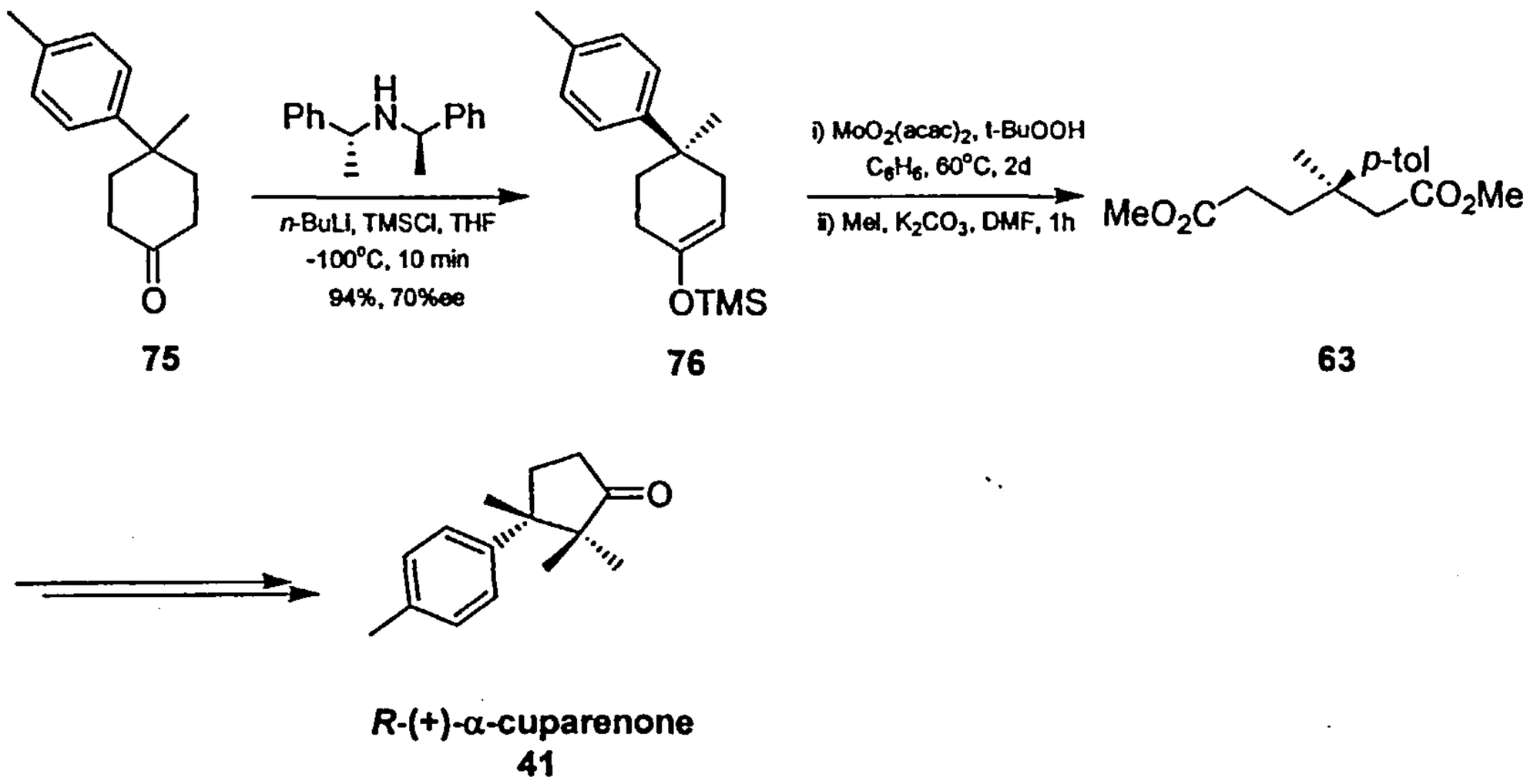
2-Alkyl or 2-aryl-2-cyclopropylidene ethanols of type **70** have been described as potentially valuable synthons for the enantioselective creation of quaternary carbons. Fukumoto *et al.*[43] reported a tandem Katsuki-Sharpless asymmetric epoxidation[44] and 1,2-rearrangement on compound **70**, to afford chiral cyclobutanones **72**,[45] giving easy access to both enantiomers of **40** and **41**. Epoxidation of **70** in the presence of *tert*-butylhydroperoxide and (+) or (–)-DET gave intermediate strained hydroxy-

oxaspiropentane **71** which underwent ring expansion via a concerted anti-1,2-rearrangement. This lead to complete transfer of chirality with inversion of configuration at the migration terminus. Substitution of the product hydroxyl group with a phenylthio group achieved by Hata's procedure[46] gave sulfide **73**. Desulfurisation with Raney-nickel afforded methyl analogue **74**, which was efficiently converted to **40** or **41** following an already established procedure (Scheme 14).[47]



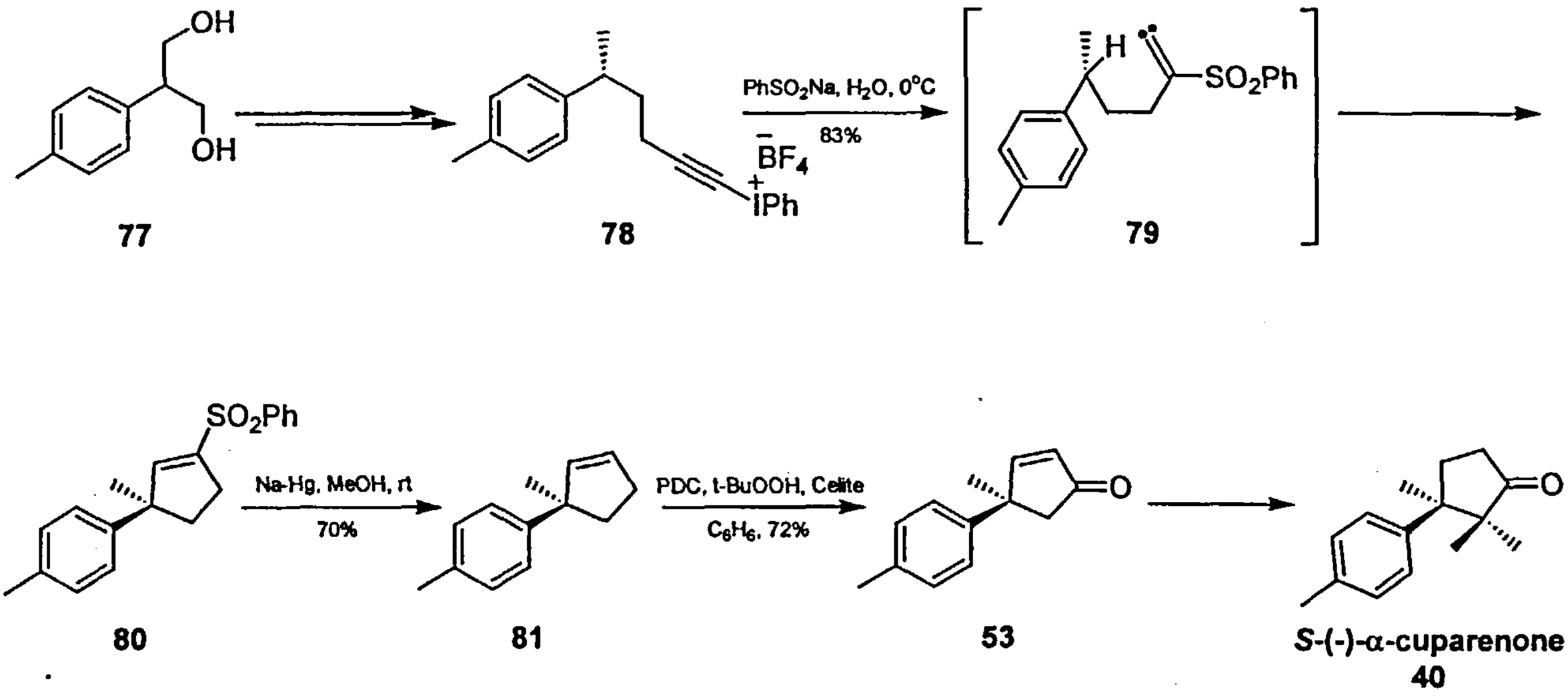
Scheme 14

Honda[48] employed an enantioselective deprotonation strategy as his key step in his synthesis of **41** from prochiral cyclohexanone **75**. Deprotonation using the anion of (*S*, S')-α,α'-dimethyldibenzylamine in the presence of TMSCl afforded the silyl enol ether **76** in 94% yield and 70% ee. Oxidative bond cleavage,[49] with molybdenyl acetylacetonate furnished the diacid, which was further esterified with methyl iodide resulting in diester **63**, the key intermediate in the Asaoka synthesis.[37]



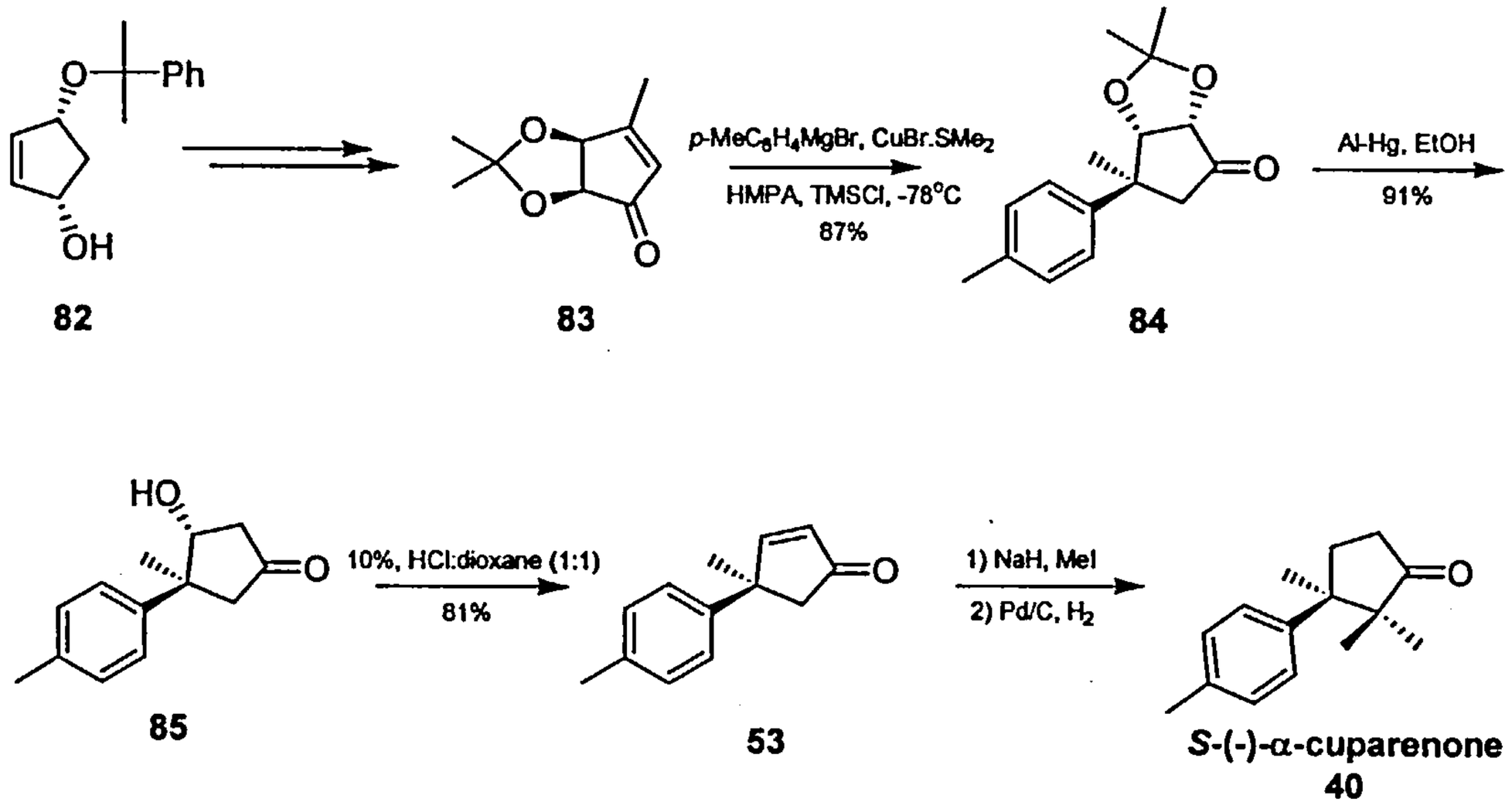
Scheme 15

Diastereoselective [1,5]-C-H insertion reaction of alkylidene carbene **79**,[50] in which the benzylic tertiary asymmetric centre was generated via a lipase-mediated asymmetric acetylation[51] of prochiral diol **77**, was applied to a synthesis of **40**. Exposure of iodonium tetrafluoroborate salt **78** to aqueous sodium benzenesulfinate at 0°C gave the cyclised vinyl sulfone **80**, via [1,5]-C-H insertion of the alkylidene carbene **79**[52] proceeding with complete retention of configuration. Removal of the benzenesulfonyl moiety in the presence of Na-Hg under sonication[53] conditions afforded **81**, which was converted to **41** via allylic oxidation[54] and dimethylation.[32]



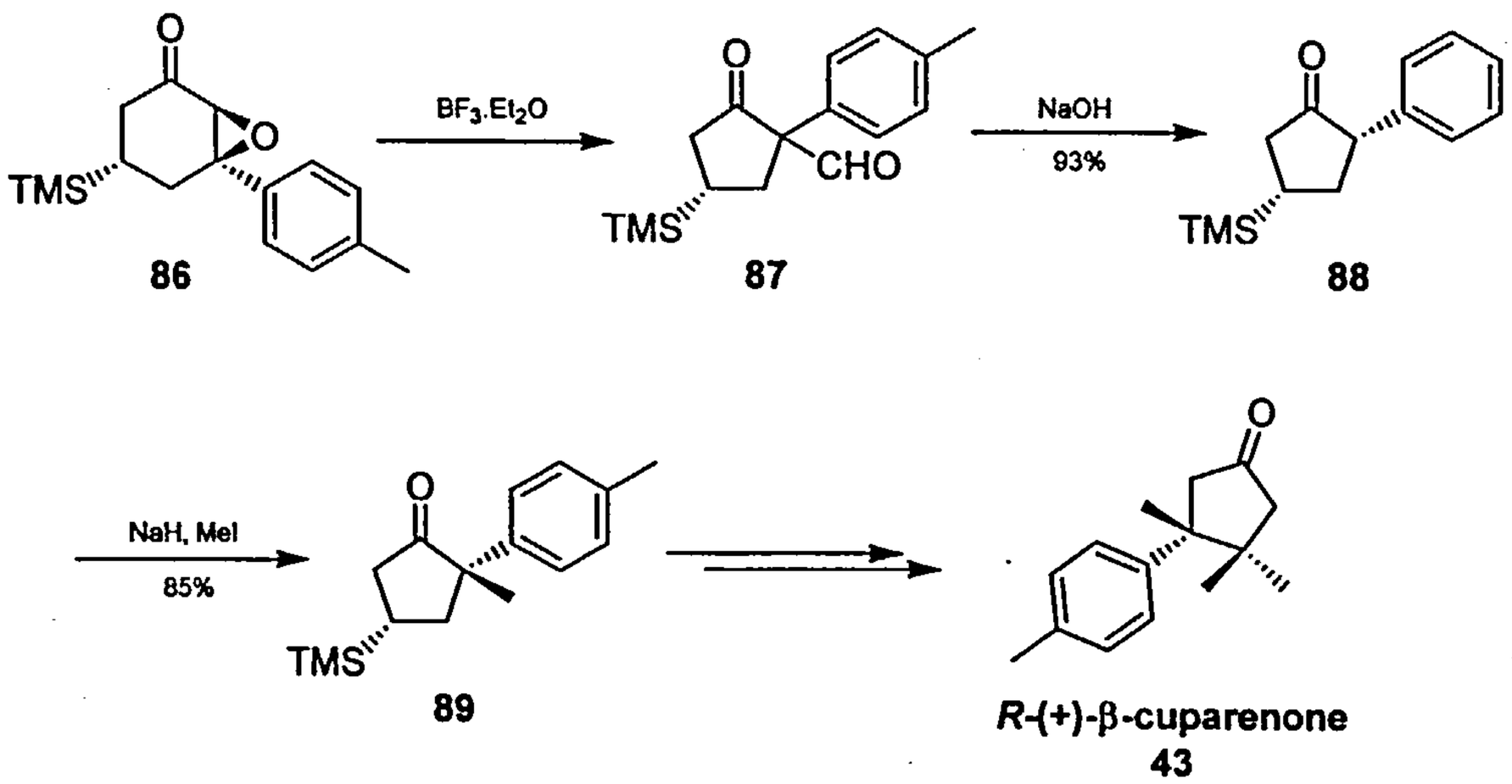
Scheme 16

Similarly conjugate addition of enone **83** with p-tolMgBr in the presence of copper (I) bromide and TMSCl allowed convex face selective 1,4 addition to yield the single cyclopentanone **84**.[55] Compound **83** was prepared via an enantioconvergent route from cyclopentanol **82**, having a latent meso structure which gave access to both **40** and **41**. Aluminium amalgam[56]-initiated α-cleavage gave the β-hydroxy ketone **85**, that was prone to β-elimination under acidic conditions. Enone **53** was then converted into **40** via an established procedure.[32]



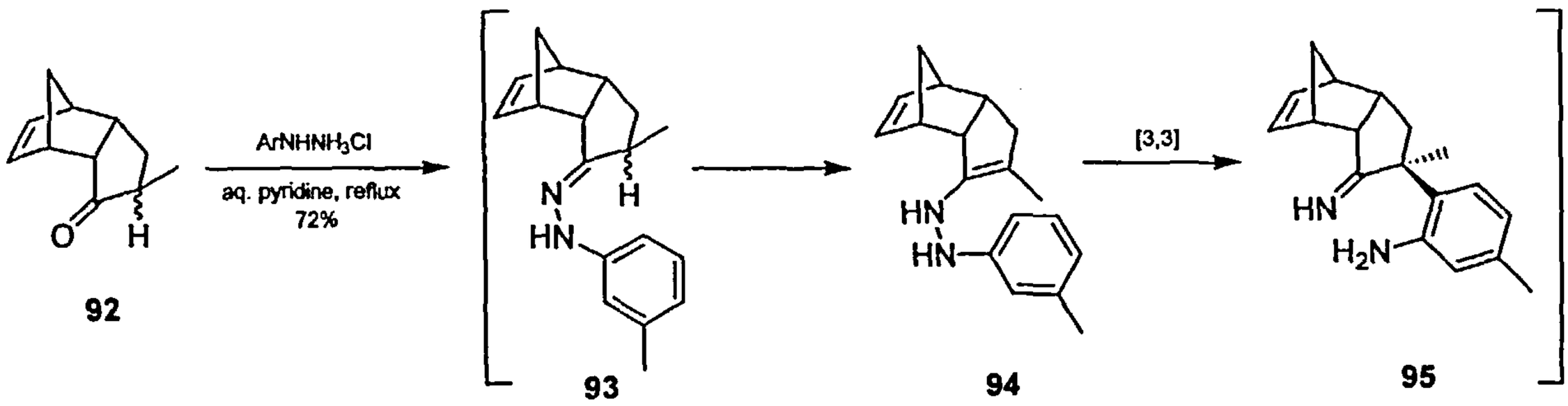
Scheme 17

Some years later Asaoka[57] extended his strategy of using TMS as a directing group towards the construction of chiral centres on alicyclic compounds. This incorporated an epoxide rearrangement[58] that enabled a synthesis **43** as well. Ring contraction of **86** by Lewis acid ($BF_3.Et_2O$) catalysed epoxide rearrangement followed by treatment with base gave the cyclopentanone **88** with high diastereomeric purity (>20:1). Diastereoselective alkylation by deprotonation with NaH followed by methylation resulted in compound **89**, which was subsequently converted to **43**.



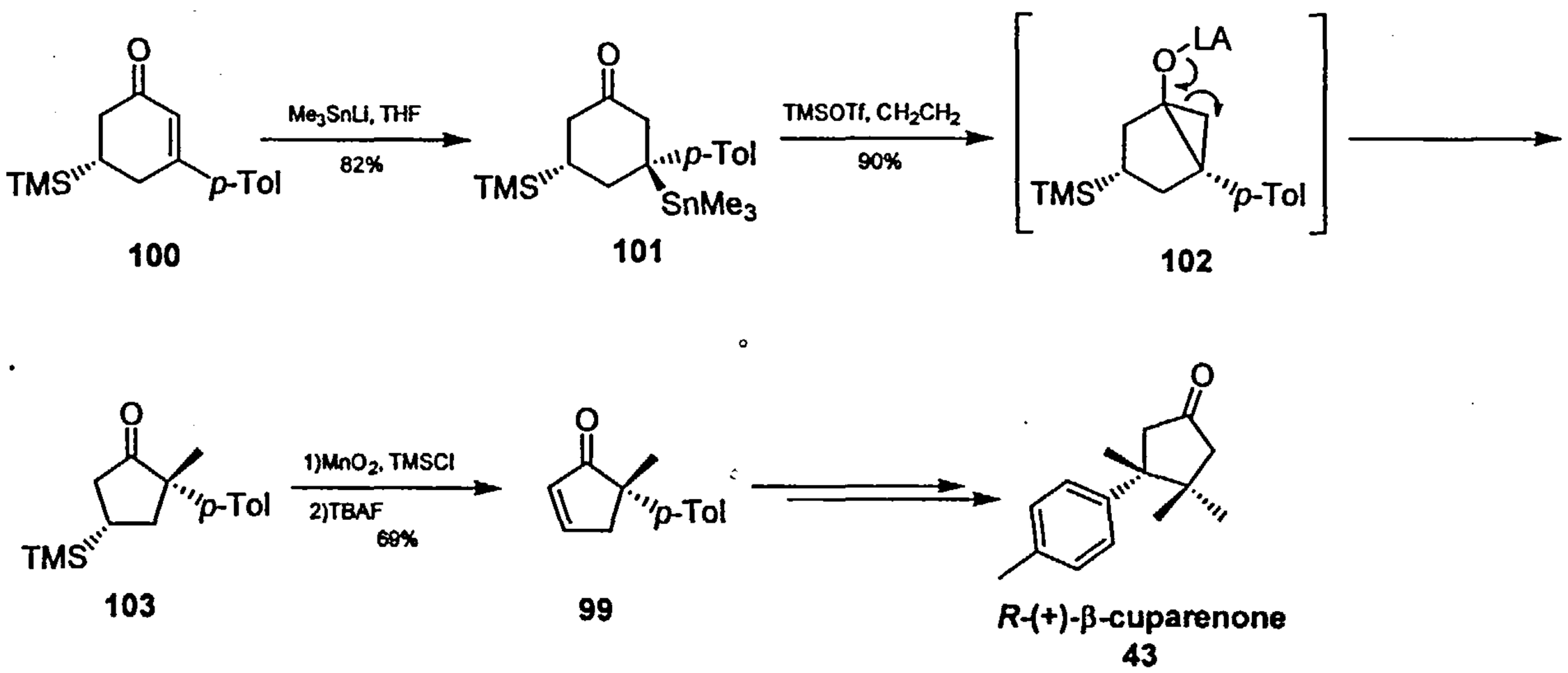
Scheme 18

Stereoselective introduction of the *p*-tolyl group at the α-position,[59] employing a Fisher indolization under non acidic conditions[60] led to a synthesis of both (–)-herbertene **110** (vide infra) and *R*-(+)-β-cuparenone **43**. Fisher indolization of optically pure dienone **92**, by introduction of the aryl group from the convex face followed by 3,3-sigmatropic rearrangement of the resulting enamine **94** gave the hemi aminal **96** as a single product. Diazotization[61] followed by a thermal retro-Diels-Alder reaction afforded the cyclopentanone **99**, which was converted to **43** via a series of reactions (Scheme 19).


ArNHNH3Cl
aq. pyridine, reflux
72%
[3,3]
92
93
94
95
-NH3
NaNO2, H3PO2, 0°C
96
97 (28%)
o-DCB, reflux
78%
99
R-(+)-β-cuparenone
43

Scheme 19

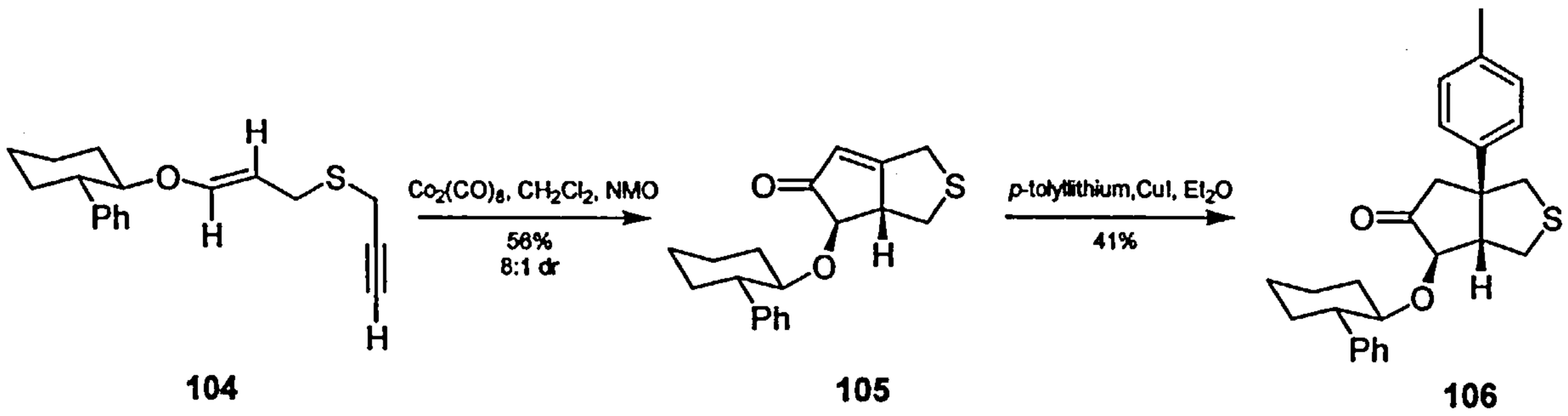
Tin-bearing carbon atoms are known to behave as latent carbanions and typically undergo reactions with cationic centres within the same molecule, resulting in cyclisations and hydride or alkyl shifts.[62] Sato[63] reported a Lewis acid induced reaction of an optically active silicon containing β-stannyl ketone **101**, as a key step in his synthesis of **43**.



Scheme 20

Requisite β-silyl-β'-stannyl ketone **101**, prepared by conjugate addition of trimethylstannylithium to compound **100**,[64] underwent a TMSOTf induced ring contraction. The stereochemical pathway proceeds with inversion at the tin bearing carbon via cyclopropanol intermediate **102**. Ring cleavage at the bond leading to the less substituted carbon formed silyl compound **103**, which was converted to **43** following a reported method (Scheme 20).[57]

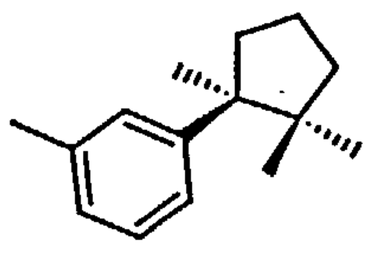
Recently Greene reported a chiral auxiliary based asymmetric intramolecular Pauson-Khand reaction as a key step en-route to **43**.[65] Exposure of (*E*)-1-alkoxy-4-thiahepten-6-yne **104** obtained as a 9:1 mixture with the (*Z*)-isomer,[66] to $Co_2(CO)_8$ in isooctane produced an 8:1 mixture of separable diastereomer **105**. Products arising from cobalt-induced bicyclisation of the (*Z*)-isomer of **104** were not detected, in accordance with the low reactivity exhibited by other *cis*-alkoxyenynes.[67] Conjugate addition of cuprate *p*-tolyl reagent, *cis* to the bridgehead hydrogen produced 7-thiabicyclo[3.3.0]octanone **106** as an 8:1 diastereomeric mixture. Subsequent Raney-nickel promoted transformation into the *vic*-dimethyl moiety **107**, followed by reductive removal[68] of the auxiliary gave **108** with 77% ee. Finally, treatment of the enolate mixture with phenylselenenyl bromide, followed by oxidation of the selenide intermediate provided known cyclopentanone **109** in moderate enantiomeric excess (Scheme 21).


Co2(CO)8, CH2Cl2, NMO
56%
8:1 dr
p-tolyllithium,CuI, Et2O
41%
Ni-raney, EtOH
95%
SmI2, THF-MeOH
90%
1) LDA, THF, PhSeBr (85%)
2) H2O2, AcOH-H2O (90%)
104
105
106
107
108
109
R-(+)-β-cuparenone

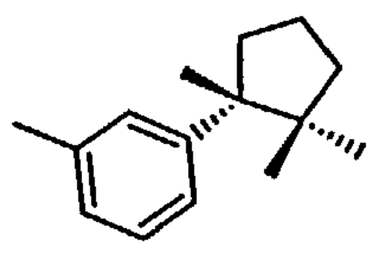
Scheme 21

1.3 Synthetic approaches to enantioenriched herbertene.

Naturally occurring (–)-herbertene **110** was first isolated by Matsuo *et al.* from the liverwort *Herberta adunca* (Dicks) S.Gray in 1981 and is the representative member of the herbertane family of sesquiterpenes. These compounds are characterised as possessing a 3-methyl-(1,2,2-trimethylcyclopentyl)cyclohexane skeleton and to date there have only been four reported syntheses in enantiopure form.



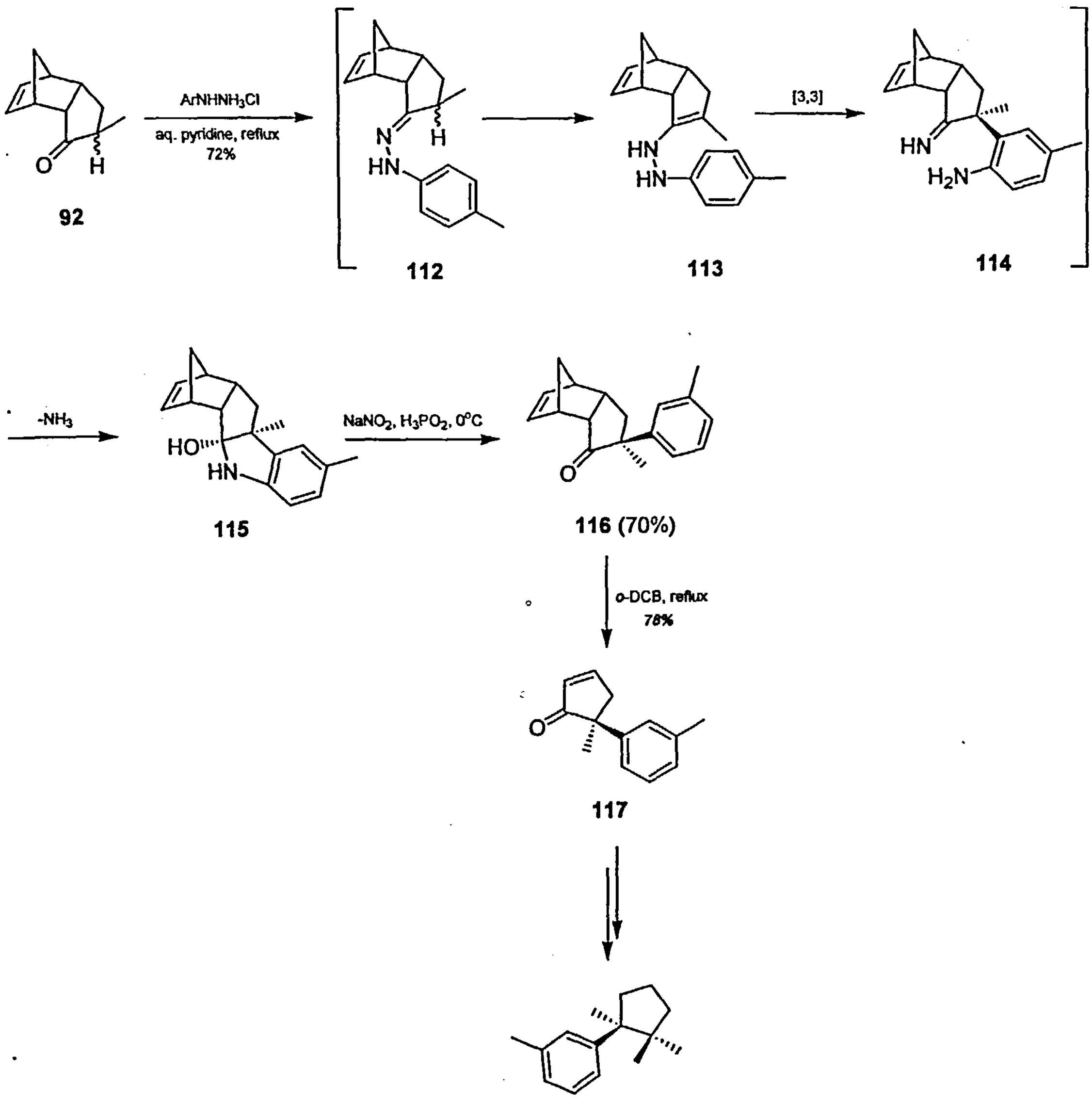
(*S*)-(-)-herbertene 110



(*R*)-(+)-herbertene 111

Figure 3

The first enantioenriched synthesis of (–)-herbertane **110** was reported by Takano and coworkers. His strategy, already disclosed in the synthesis of *S*-(+)-β-cuparenone **43** (Scheme 19), was also successfully applied to the syntheses of **110**. The quaternary stereocentre in **110** was produced by stereoselective introduction of a *p*-tolyl group at the α-position of **92** followed by Fisher indolization (Scheme 22).



92 112 113 114

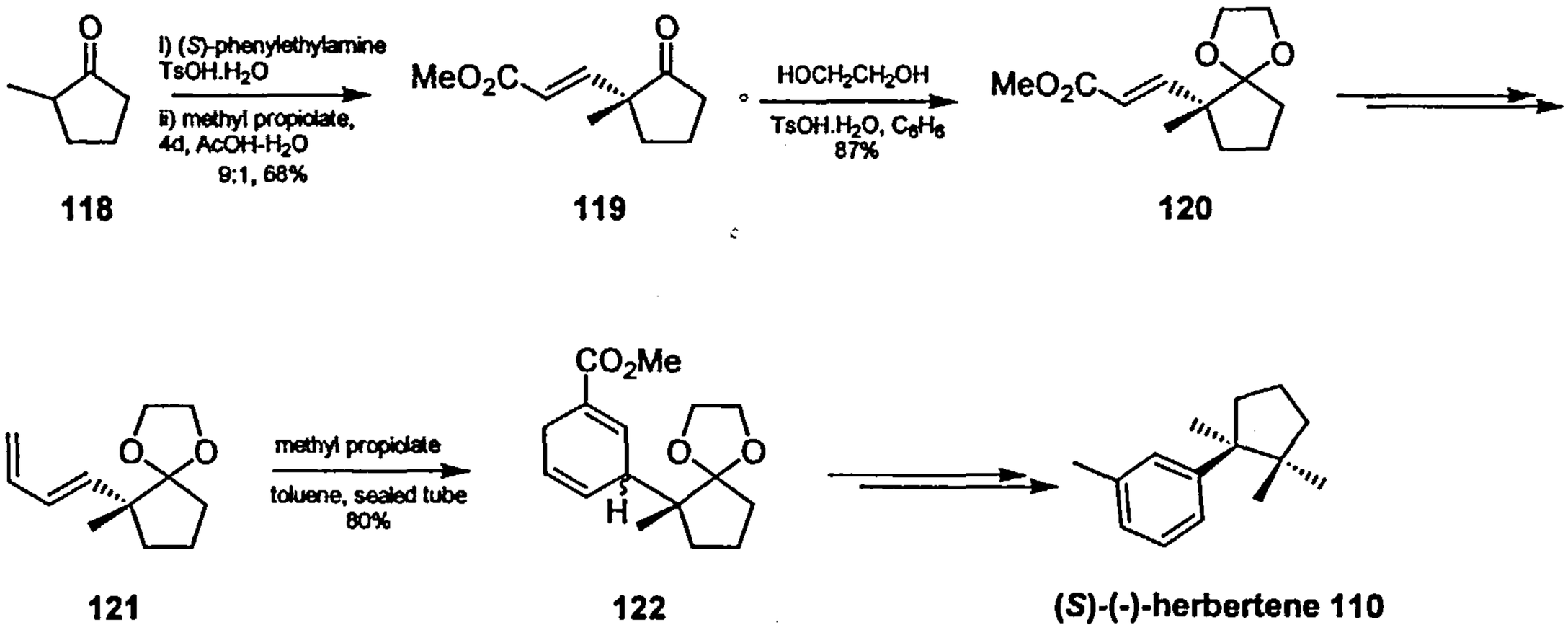
115 116 (70%) 117

(*S*)-(-)-herbertene 110

Scheme 22

Soon after this Tori[69] reported a synthesis of **110** based on a Diels-Alder reaction and using phenylethylamine as a chiral auxiliary. Imination of **118** with (*S*)-phenylethylamine followed by alkylation of the equilibrating enamine with methyl propiolate[70] gave keto ester **119** in 68% and 71% ee. When carried out using methyl acrylate under Pfau's conditions the same keto ester could be obtained in higher

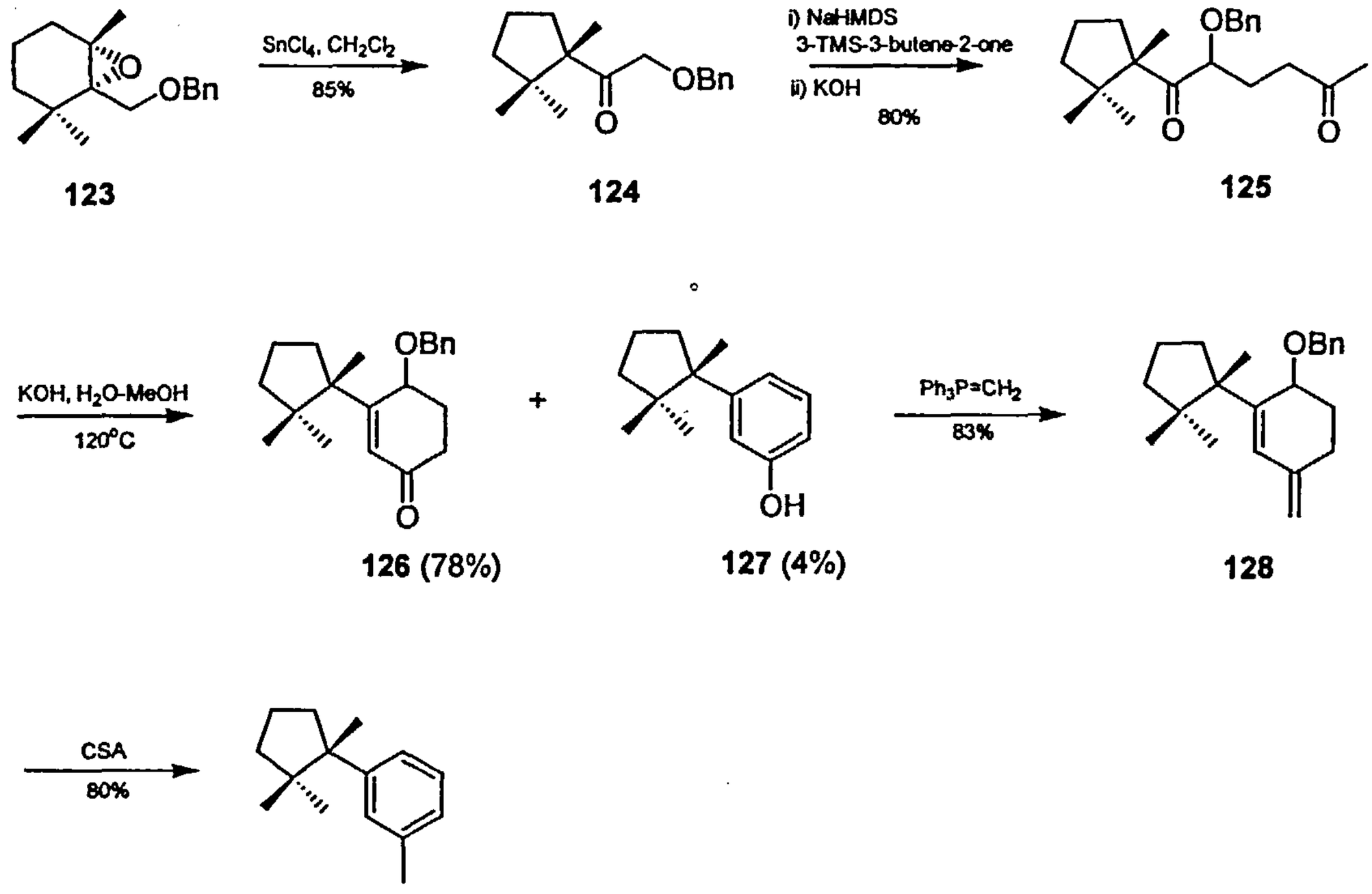
enantiomeric purity (75%, 94% ee), however this required a greater number of steps.[71] The diene **121** prepared in 4 steps from **120** was then subject to a regioselective Diels-Alder reaction to give **122** as a 3.5:1 mixture of adducts. DDQ oxidation, removal of the ketal,[72] cyclopropanation[73] of the exomethylene product and straightforward reduction and hydrogenation furnished **110**. The specific rotation (α_D=-25.7) of **98** prepared in this manner did not match that reported[74] (α_D=-48.3) presumably due to the reduced enantiomeric purity of **119** (Scheme 23).



Scheme 23

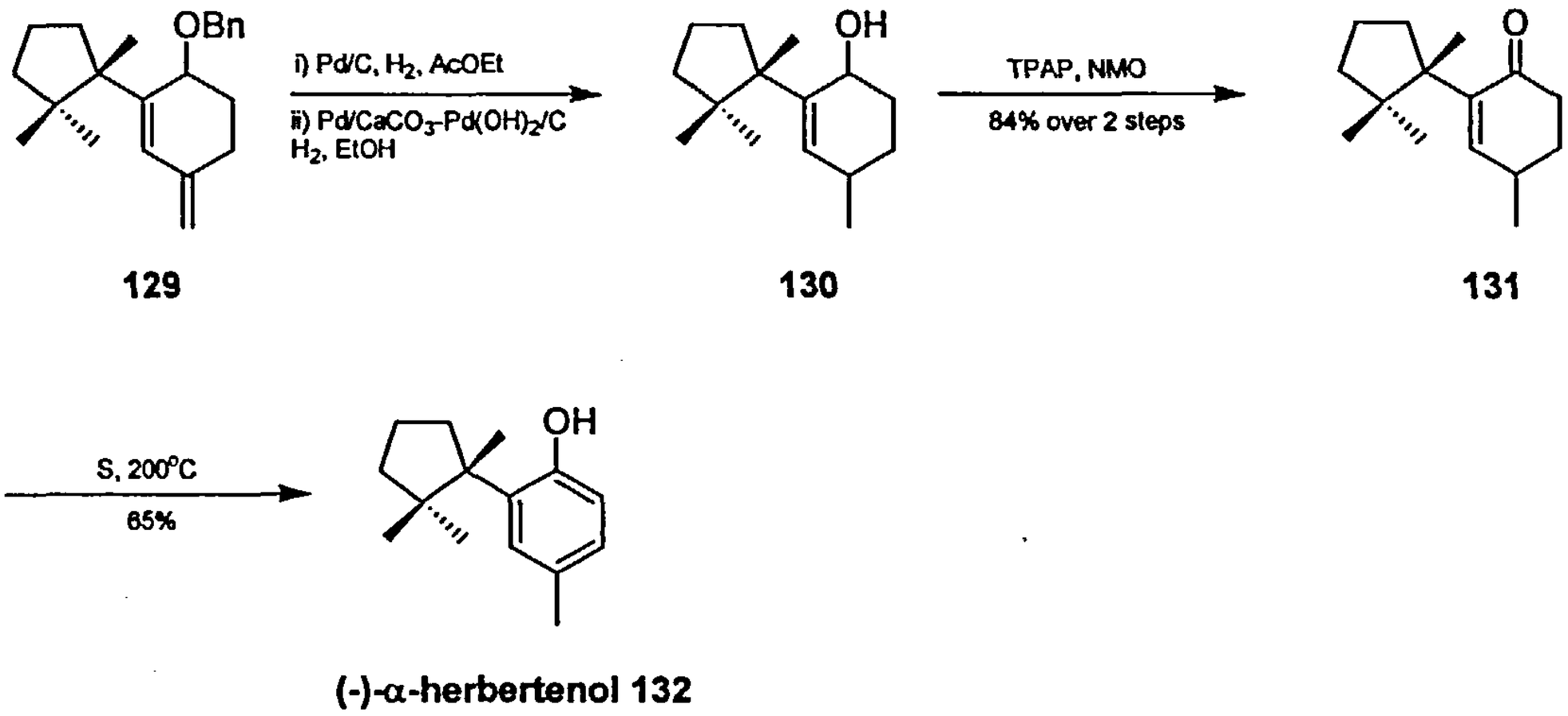
Adaptation of the chemistry already delineated in scheme 2 also led to a synthesis of (–)-herbertene **110** and (–)-α-herbertenol **132**.[75] Tin (IV) chloride promoted pinacol rearrangement of **123**, this time with the benzyl ether[76] gave α-benzyloxy ketone **124** in 85% yield and with no loss of optical activity (98% ee). Completion of the cyclohexane ring was achieved by treatment of the sodium enolate of **124** with α-trimethylsilyl moiety to give benzyloxy ketone **125** in 80% yield as a 1:1 mixture of diastereomers. This was of no consequence, since the chiral centre was lost during subsequent transformations. Intramolecular aldol cyclisation under basic conditions in a sealed

tube afforded an epimeric mixture of cyclohexanone **126** in 78% yield, together with 4% of separable phenol **127**. Standard Wittig methylation and CSA assisted isomerisation of the exocyclic double bond in **128** to the endocyclic position, followed by elimination of the benzyloxy moiety produced (*S*)-(–)-herbertene **110** in 28% yield over 7 steps from β-cyclogeraniol **11** (Scheme 24).



Scheme 24

On the other hand chemoselective hydrogenation of the exocyclic double bond in **129**, followed by hydrogenolysis[77] of the benzyl group resulted in the formation of diastereomeric allylic alcohols **130**, which after oxidation and aromatisation gave (–)-α-herbertenol **132** in 19% yield over 10 steps (Scheme 25).

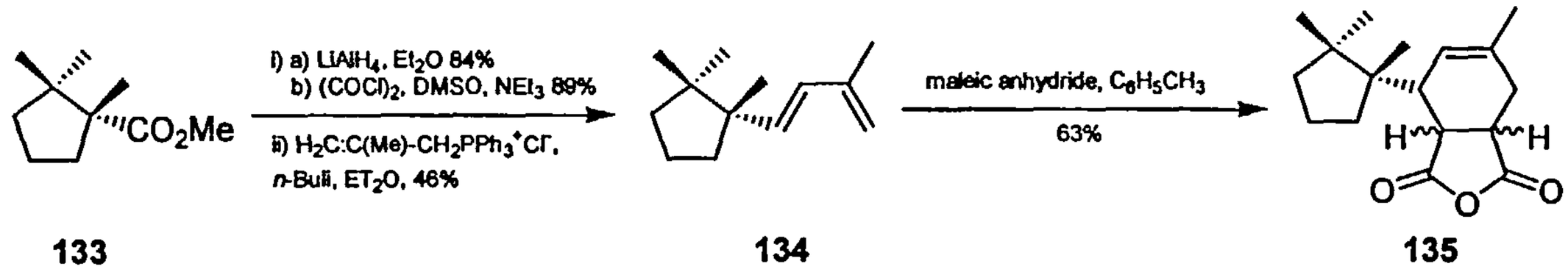


129 **130** **131**

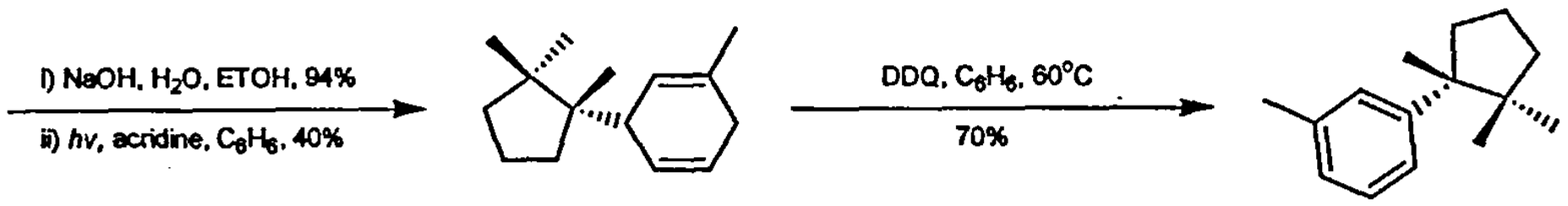
(-)-α-herbertenol 132

Scheme 25

Ghosh[78] reported the first synthesis of (+)-herbertene **111**. His approach relied upon a Diels-Alder reaction on diene **134**, prepared from ester **133**, which in turn was derived from commercially available camphoric acid. Attempts to synthesise enantiopure ester **133** via regioselective and stereospecific electronically-controlled pinacol rearrangement of alkoxycyclobutane derivatives was unsuccessful due to a problematic enzymatic resolution step.[78,79] Gratifyingly however, selective hydrolysis of the dimethyl ester of camphoric acid followed by photo-induced decarboxylation of the acid gave **133**, which was converted into the diene **134**. Diels-Alder reaction of **134** with maleic anhydride afforded adducts **135** as an inseparable mixture of diastereomers in a 1:2 ratio. Hydrolysis of the anhydride mixture followed by photodecarboxylation[80] afforded diene **136**, which was aromatised with DDQ to furnish (+)-herbertene **111** with $[\alpha]_D^{30}$= +56.3 (*c* 0.54, $CHCl_3$) (Scheme 26).



133 134 135



136 (*R*)-(+)-herbertene 111

Scheme 26

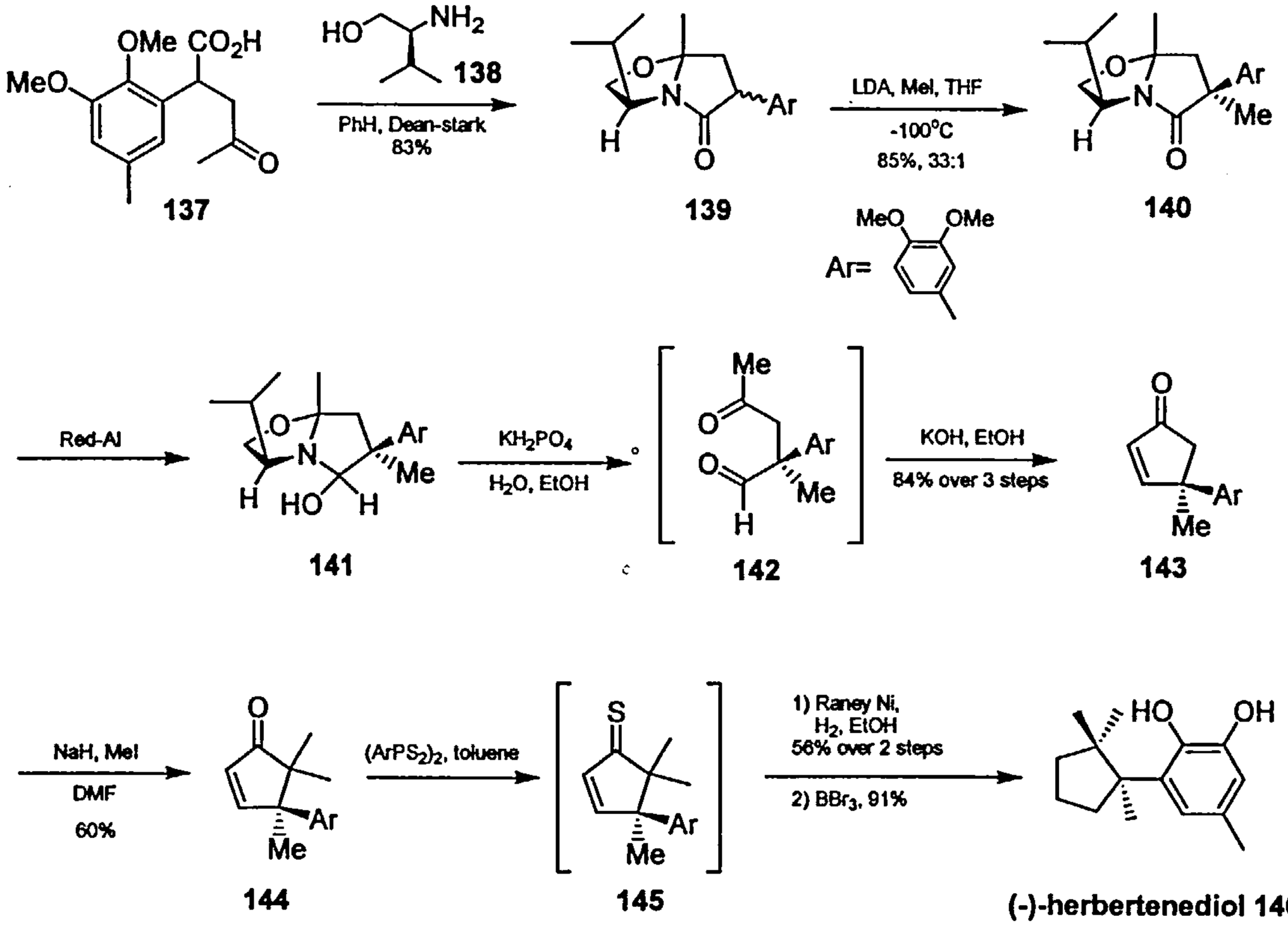
1.4 Synthetic approaches to enantioenriched herbertenediol.

Other herbertane type sesquiterpenes have been isolated from a wide variety of liverworts. This includes α-herbertenol **132** mentioned earlier, herbertenediol and the more complicated dimeric phenols, the mastigophorenes A, B, C and D. Asakawa[81] reported the isolation of the latter compounds from *Mastigophora diclados* (Brid.) Nees, a rather primitive liverwort found in topical Asiatic regions.[82] Some of these compounds can also be found in other liverworts belonging to the genus *Herbertus*, *Herberta adunca*,[2] *Herbertus aduncus*,[83a] and *Herberta sakuraii*.[80b]

In addition to the racemic syntheses[84] of herbertenediol **146** and apart from the reported oxidation of α-herbertenol **132**,[85] there are relatively few reported asymmetric syntheses of **146**, despite its interesting biological activity.[81]

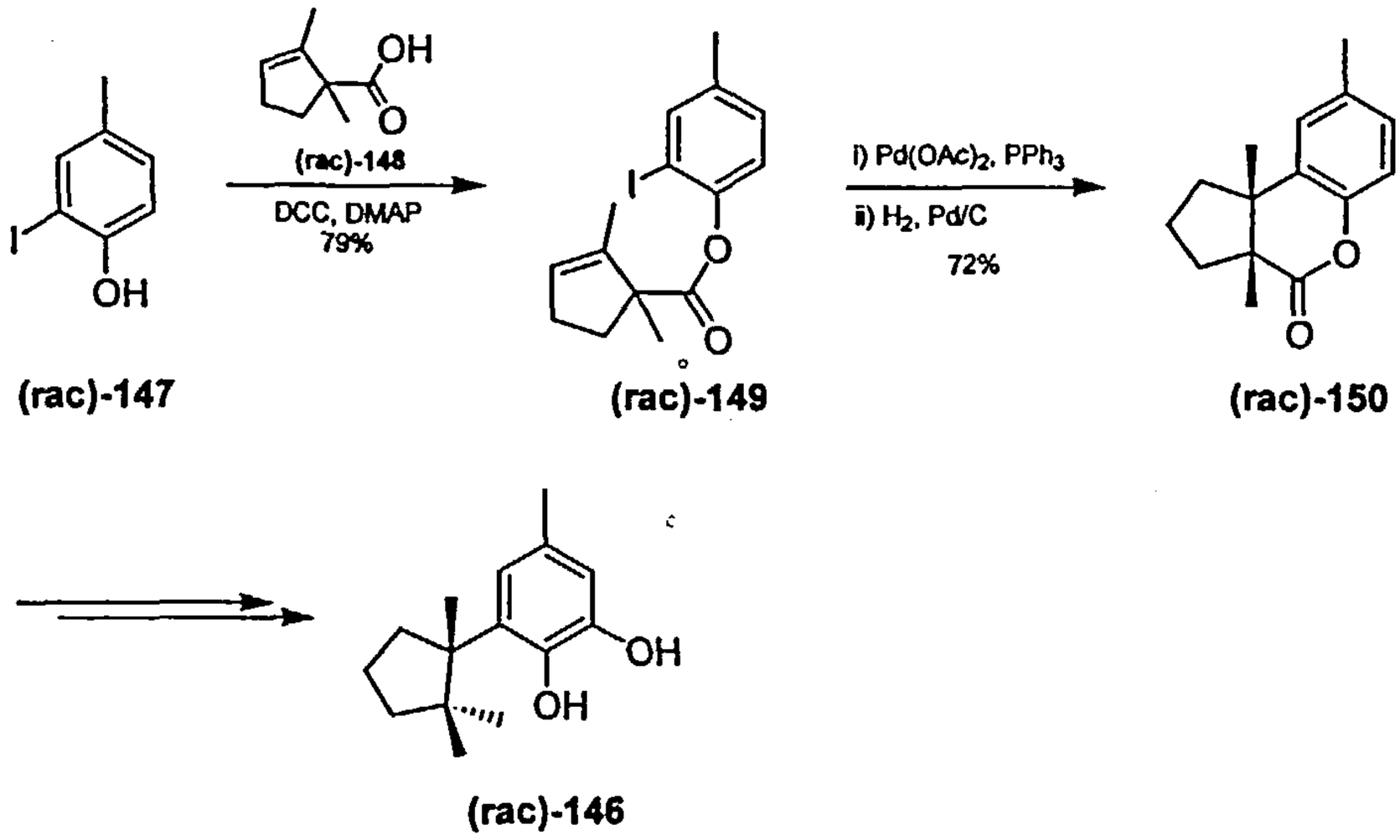
The first total synthesis of herbertenediol **146** was reported by Meyers.[86] Extension of the chiral bicyclic lactam methodology already described in scheme 9, gave (–)-herbertendiol **146** which was also used towards the synthesis of (–)-mastigophorenes A and B. Condensation of keto acid **137** with (*S*)-valinol **138** gave the bicyclic lactam **139** as a 3:2 mixture of epimers. Deprotonation of either epimer gave rise to the same enolate, which was alkylated from the endo face using methyl iodide to afford after recrystalisation the endo-alkylated product **140** as a single diastereomer. Reduction of the bicyclic lactam moiety followed by hydrolysis with the phosphate buffer gave the keto aldehyde **142**. Base-induced cyclization afforded the cyclopentanone **143**, which was subjected to dialkylation and subsequent reduction via thioenone **145**. Finally,

conversion of the methoxy groups on the aromatic ring to hydroxyl moieties gave (–)-herbertenediol **146** in good optical purity (Scheme 27).



Scheme 27

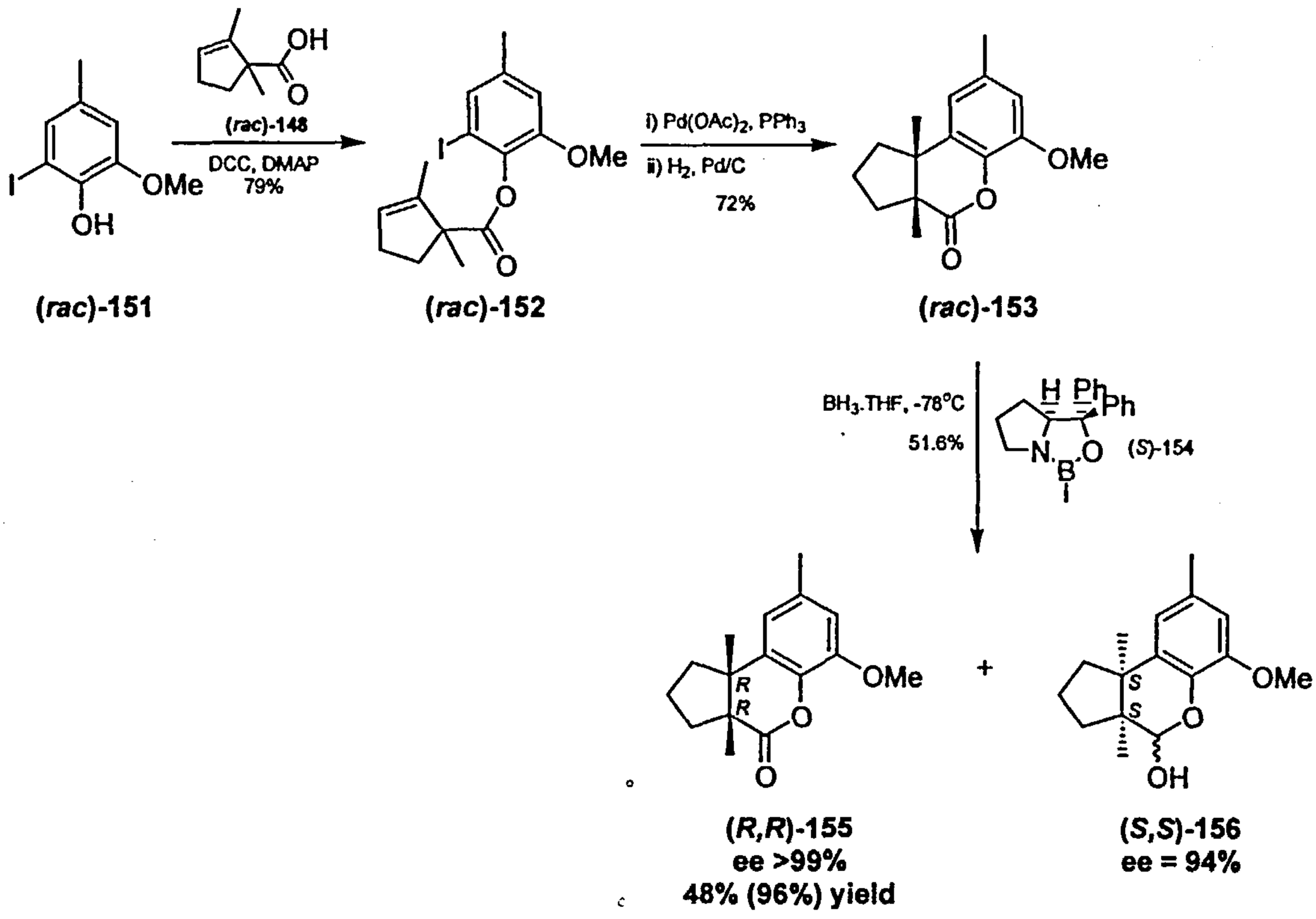
Bringmann[87] formed enantiopure herbertenediol **146** by a novel kinetic resolution of lactones. His method was related to a previously reported pathway by Fukuyama[88] albeit in racemic form. The chiral quaternary carbon was built up by a diastereoselective intramolecular Heck reaction of **149** to give lactone **150**, which was then transformed to *rac*-**146** (Scheme 28).



Scheme 28

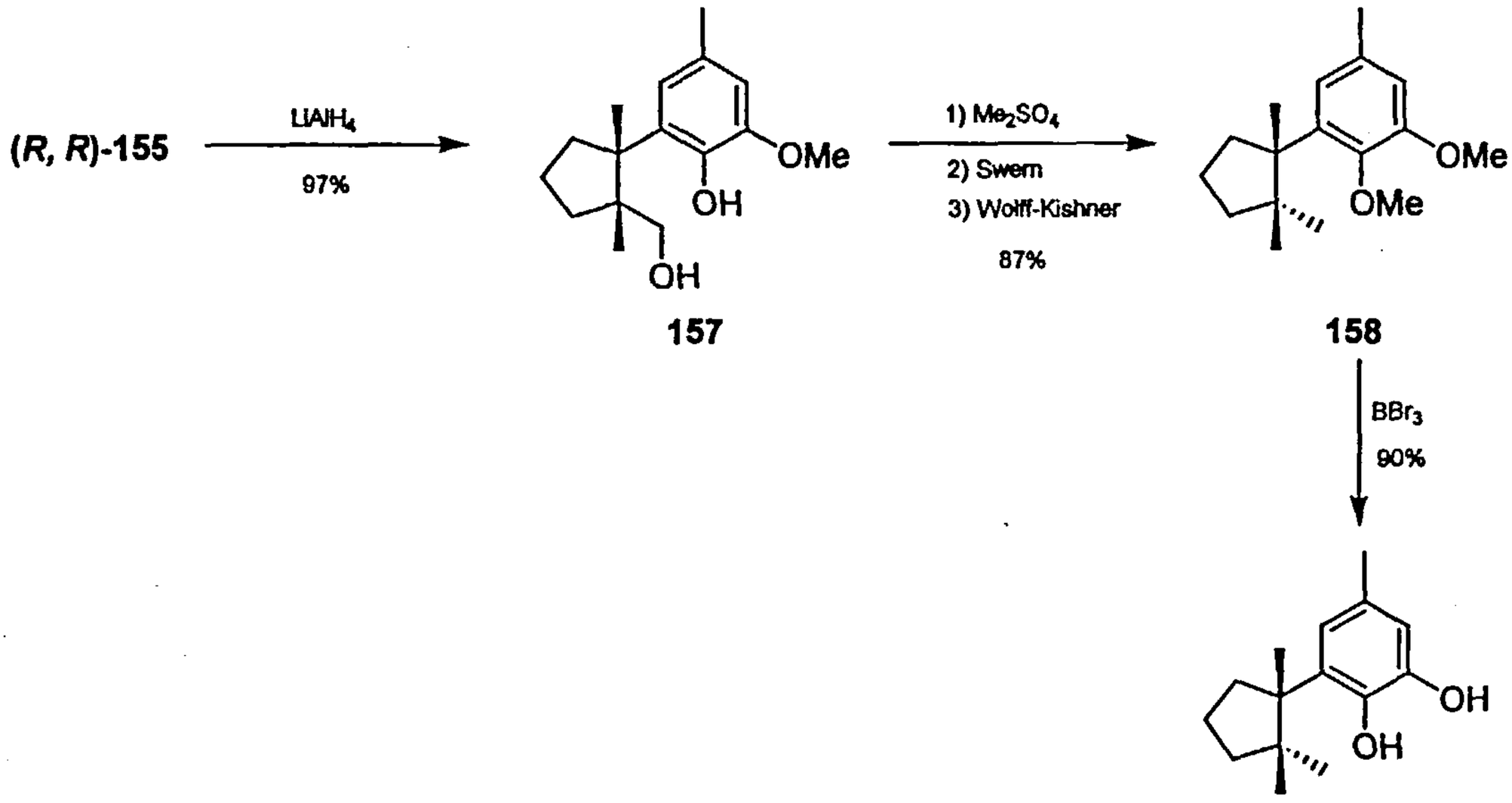
Although the synthesis was regarded to constitute a formal total synthesis of enantiopure (–)-herbertenediol **146**, the acid **148** required in stereochemical homogenous form had only been synthesised in 90% enantiomeric purity.[89]

Modification by Bringmann of this synthetic pathway, firstly by starting directly with the di-oxygenated aromatic building block **151**[90] and secondly exploiting a kinetic resolution step employing an enantiomer-differentiating oxazaborolidine-mediated borane reduction on *rac*-**153**, conveniently furnished the lactone (*R*, *R*)-**155** in 51% conversion and >99% ee.



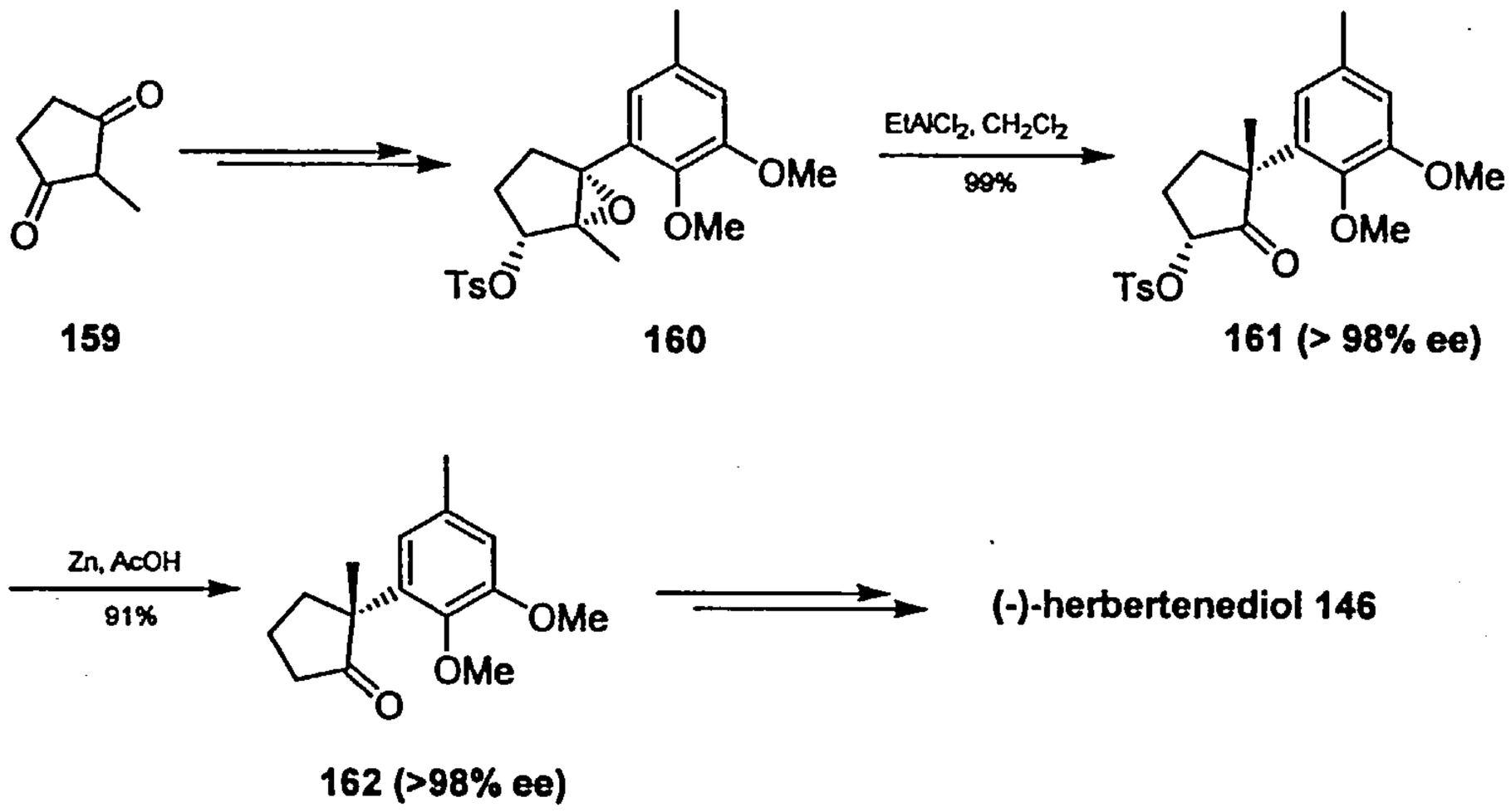
Scheme 29

Enantiopure (–)-herbertendiol **146** was synthesised from (*R*, *R*)-**155** by following an analogous procedure described for the racemic material by Fukuyama[88]. Reduction of (*R*, *R*)-**155** with $LiAlH_4$ gave the diol **157**, which was converted to herbertenediol precursor **158** by protection of the phenolic function as its methyl ether, Swern oxidation and Wolff-Kishner reduction. Finally, deprotection of the dimethyl ether groups in **158** with BBr_3 led to enantiopure (–)-herbertendiol **146** (Scheme 30).



Scheme 30

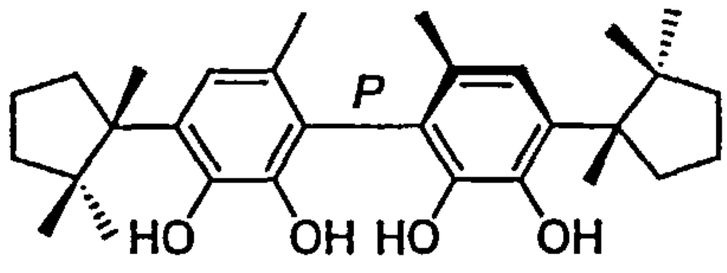
Kita has employed an epoxy sulfonate rearrangement as the key step in the construction of the chiral quaternary centre. The key intermediate **160** prepared from compound **159**, which contains a sulfonyloxy electron withdrawing group has been shown to undergo a rearrangement via Lewis acid promoted β-cleavage of the oxirane ring and 1,2-methyl migration. The resulting α-keto tosylate **161** was converted to optically active **162** by reductive removal of the tosyloxy functionality. Further transformations including dimethylation of the ketone in **162** gave (–)-herbertenediol **146** in >98% ee and 44% overall yield, starting from commercially available methylcyclopentane-1,3-dione **159** (Scheme 31).


O
O
159
TsO
O
OMe
OMe
160
EtAlCl2, CH2Cl2
99%
TsO
O
OMe
OMe
161 (> 98% ee)
Zn, AcOH
91%
OMe
OMe
O
162 (>98% ee)
(-)-herbertenediol 146

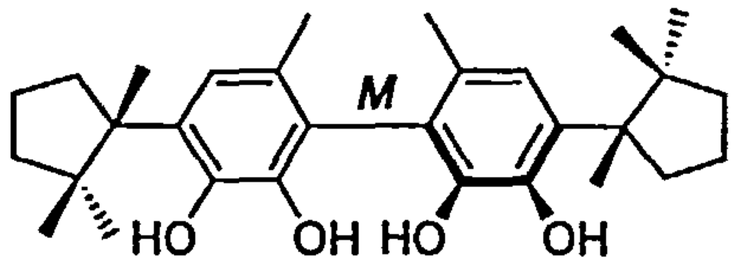
Scheme 31

1.5 Synthetic approaches to enantioenriched mastigophorene A and B.

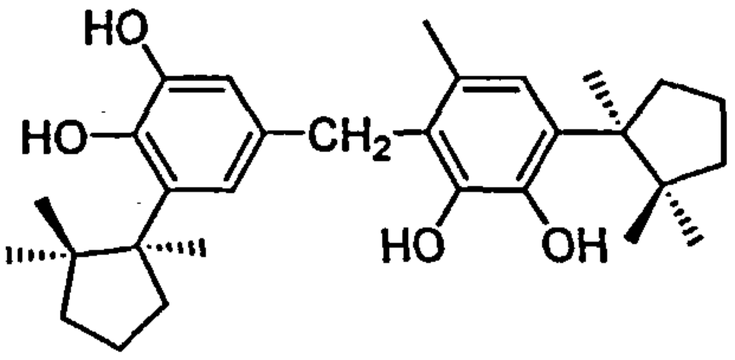
The C_2-symmetric-"dimeric" sesquiterpenes from *Mastigophora* liverworts have also attracted considerable interest over the past few years, resulting in a number of publications.[91] This is not only due to their intriguing neurotrophic properties but also the challenge of controlling both elements of axial and centro chirality. Mastigophorenes A, B and D were found to promote neuronal outgrowth and enhance acetyltransferase activity in the cerebral hemisphere of fetal rats. Cell culture experiments have indicated mastigophorenes A and B to not only promote neurite outgrowth but also maintain neuronal survival, suggesting that they could protect the neurons from damage by toxic substances such as oxygen free radicals.[92] These compounds are regarded as promising therapeutic agents for degenerative diseases such as Parkinson's and Alzheimer's.[93] Fukuyama has proposed a biosynthetic pathway to the four dimers co-occurring in the liverwort via a one electron oxidative phenolic coupling of (–)-herbertenediol **146**.[2b] To date there have been three reported asymmetric synthesis of mastigophorenes A and B all not surprisingly incorporating **146** as one of their key intermediates.



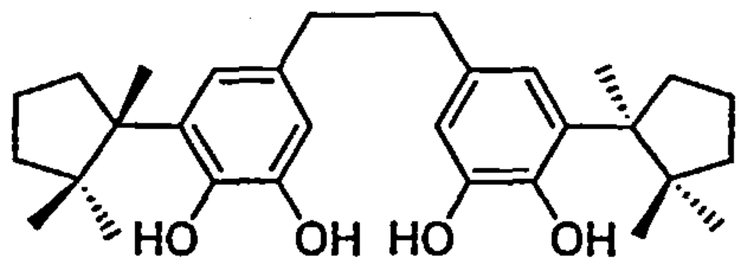
(-)-mastigophorene A (163)



(-)-mastigophorene B (164)



mastigophorene C (165)



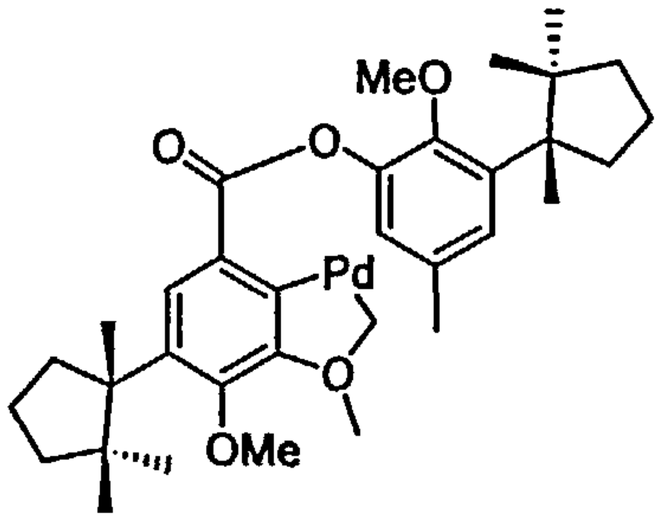
mastigophorene D (166)

Figure 4

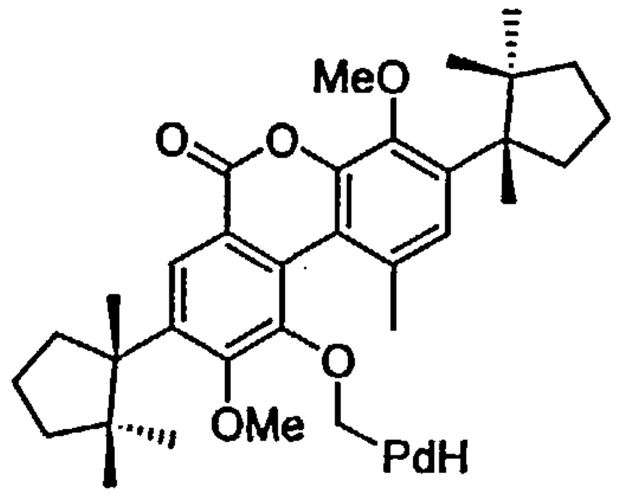
A two-fold application of the "lactone concept" by Bringmann et.al,[94] firstly to establish the chiral molecular half of mastigophorene that is (–)-herbertenediol (vide supra) and secondly to control the axial or atropo-diastereoselectivity via a dynamic kinetic resolution of an unstable biaryl lactone has been applied to give optionally mastigophorene A [(*P*)-**163**] and B [(*M*)-**164**] in good enantiomeric purity (Scheme 32).[95]

Coupling of phenol **170** via its phenolate to acid chloride **169** gave the bromo ester **171** which underwent an intramolecular biaryl coupling reaction to afford the key biaryl lactones in moderate to poor yield (39%). Further attempts to increase the yield through longer reaction times, variation of the catalyst and solvent all resulted in failure. Although there is no direct evidence, reasoning suggests this might be due to the methoxy group ortho to the halogen, which could undergo C-H activation,[96] thus resulting in a five membered palladacycle **167** or compound of type **168**, which could

be responsible for the poor coupling yields (Figure 5). Reaction of the rapidly interconverting atropo-diastereomers **172** and **173** under Corey-Bakshi-Shibata (CBS) reduction conditions[97] produced the corresponding diols (*P*)-**176** and (*M*)-**177** depending on the type of oxazaborolidine used. Further transformations of (*P*)-**176** and (*M*)-**177** gave mastigophorenes A **163** and B **164** respectively, [98] which were fully identical spectroscopically with the natural product (Scheme 32).[99]

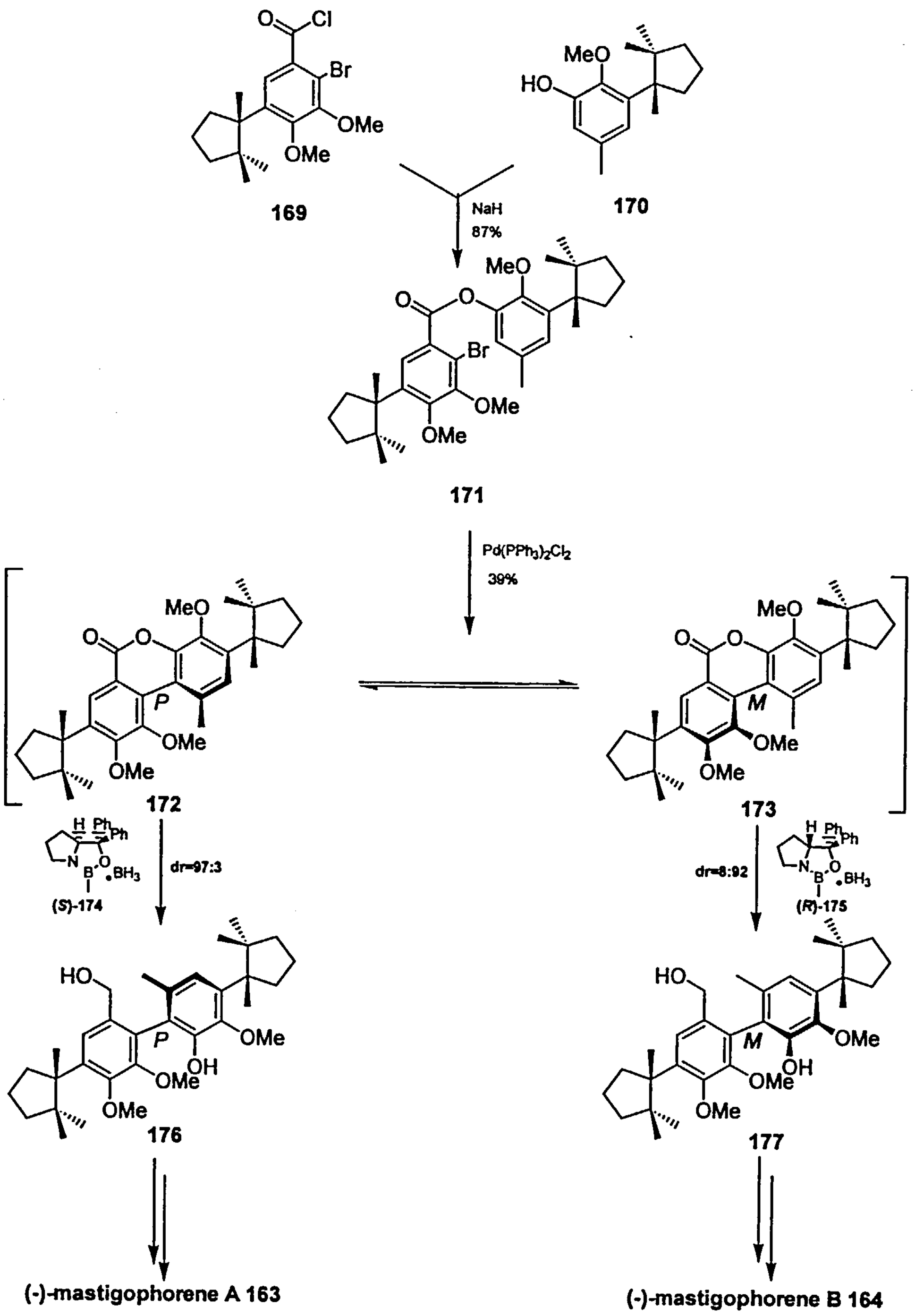


167



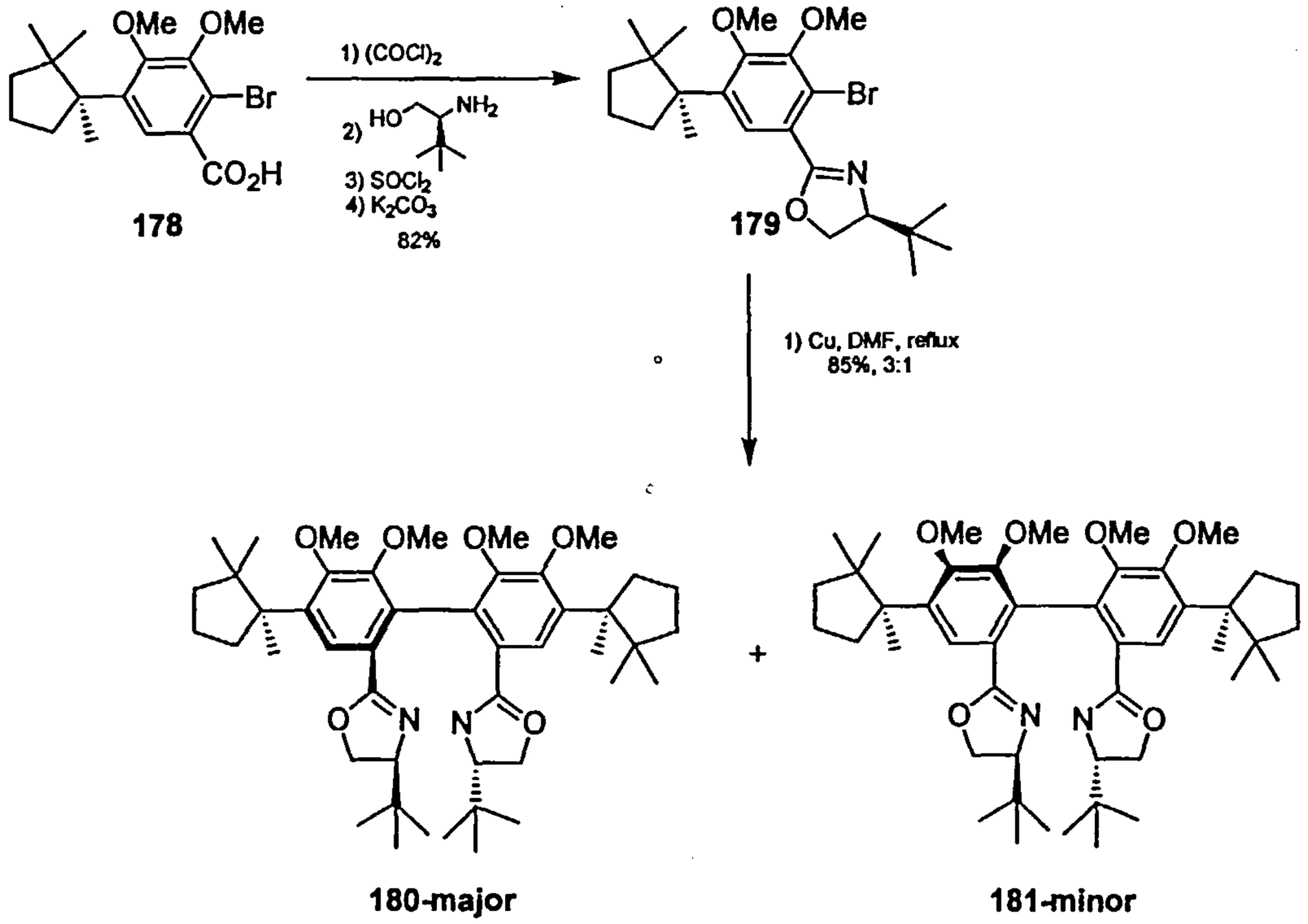
168

Figure 5


O
Cl
Br
OMe
OMe
169
MeO
HO
170
NaH
87%
MeO
O
O
Br
OMe
OMe
171
Pd(PPh3)2Cl2
39%
MeO
O
O
P
OMe
OMe
172
MeO
O
O
M
OMe
OMe
173
H
Ph
Ph
N
B
O
•BH3
(S)-174
dr=97:3
H
Ph
Ph
N
B
O
•BH3
(R)-175
dr=8:92
HO
P
OMe
OH
OMe
OMe
176
HO
M
OMe
OH
OMe
OMe
177
(-)-mastigophorene A 163
(-)-mastigophorene B 164

Scheme 32

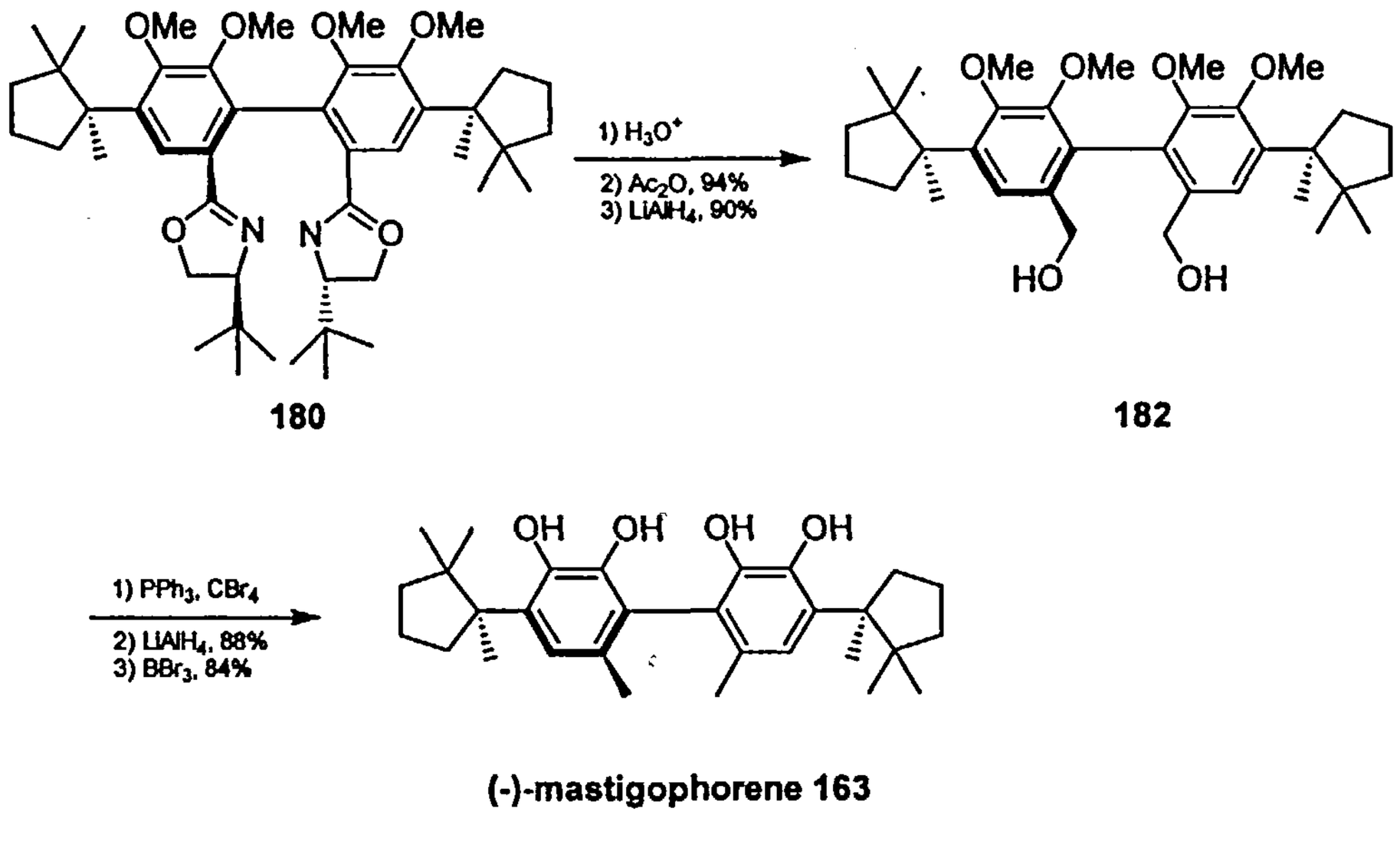
Meyers on the other hand established chirality about the biaryl axis via an oxazoline mediated Ullmann coupling on (-)-herbertenediol **146**.[86] Chemical manipulation of (-)-**146** to acid **178**[100] followed by transformation of the acid moiety into the (*S*)-*tert*-leucinol gave the key aromatic oxazoline precursor **179**.[101]



Scheme 33

Ullmann coupling of **179** using Cu in DMF proceeded with little atroposelectivity in the early stages. However, under reflux conditions an equilibrium mixture containing a 3:1 ratio of diastereomers **180** and **181** was achieved. The observed selectivity is thought to correspond to the relative stability of the initially formed copper complexes which lead to **180** and **181**. Unfavourable complexation leading to the minor diastereomer **181** due to steric interaction between the *tert*-butyl groups was exploited during the separation step. Chromatography of the crude coupling mixture gave uncomplexed **181** and

copper-complexed **180** that was washed with NH_4OH to afford diastereomerically pure bisoxazoline **180** (Scheme 33).



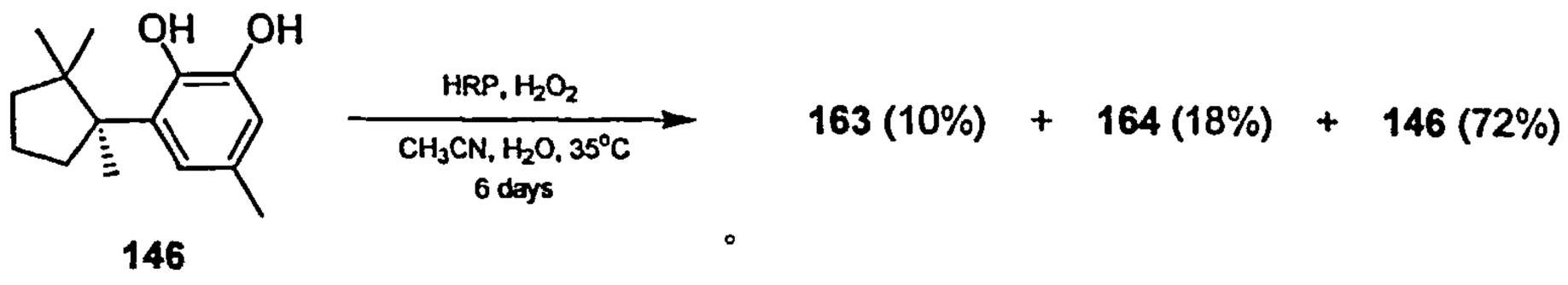
180 **182**

(-)-mastigophorene 163

Scheme 34

Removal of the chiral oxazoline moieties highlighted in scheme 34 provided (–)-mastigophorene A **163** with an observed rotation = -68 (*c* 0.4, $CHCl_3$); literature value = -65 (*c* 0.4, $CHCl_3$). The preparation of (-)-mastigophorene B **164** followed a similar sequence of events, replacing the auxiliary with the less expensive (*R*)-valinol provided even higher diastereoselection during the Ullmann coupling step (6.7:1). Subjection to the above sequence gave mastigophorene B **164** which was identical to the natural product.[2b]

More recently Fukuyama et al.[92] has reported an enzymatic phenolic coupling of **146** to yield dimers **163** and **164** directly. Horseradish peroxidase (HRP) catalysed oxidative coupling of **146** in acetonitrile at pH 6.0 resulted in a separable mixture of **163** and **164** alongside recyclable **146**. Although the yields are low and reaction times long, it is by far one of the simplest operations developed towards the synthesis of **163** and **164** (Scheme 35).



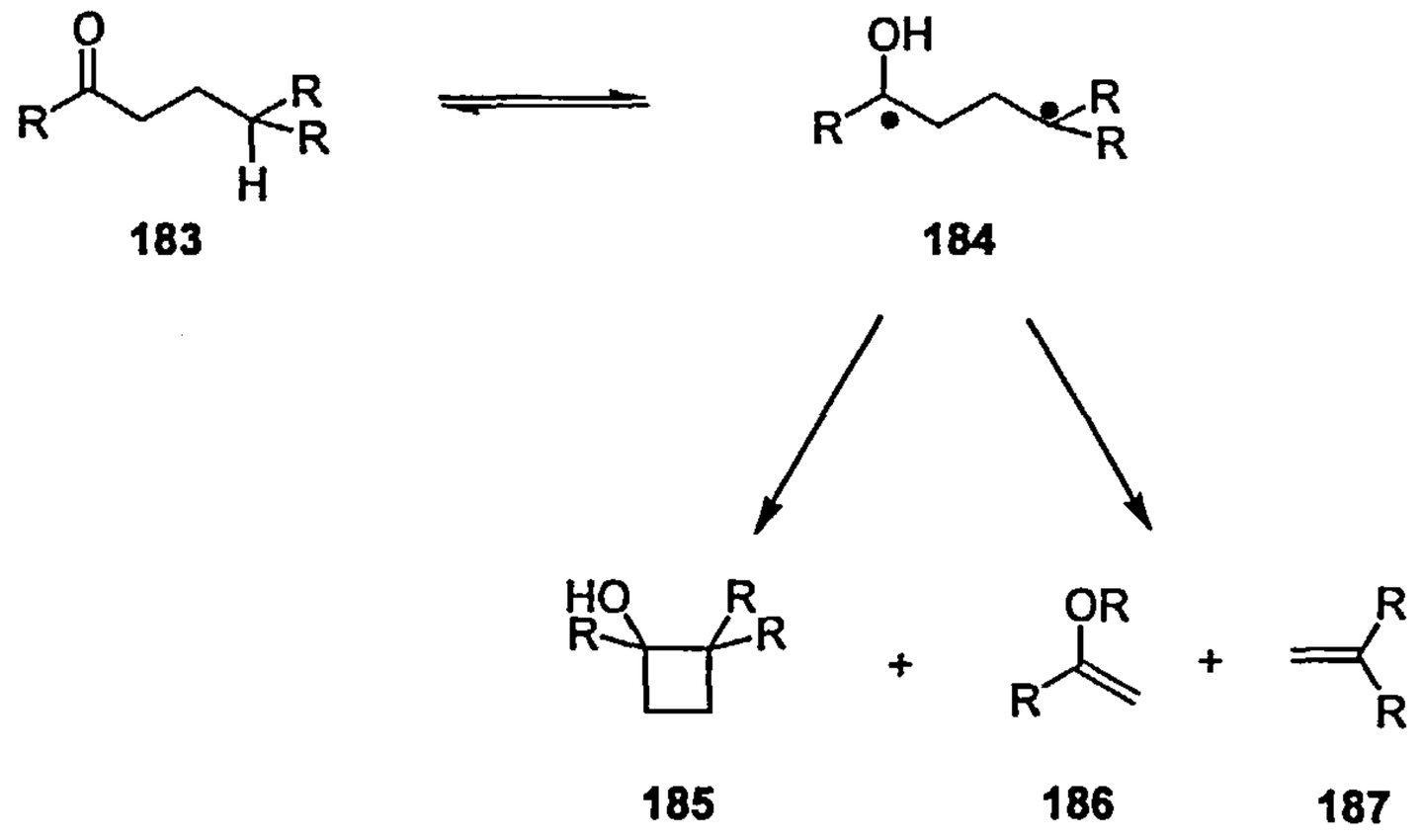
146

Scheme 35

1.6 Photochemistry of alkenes and amines.

In recent years photochemical processes, operating via single electron transfer (SET) have become a topic of considerable interest. This has been demonstrated by the large number of reviews summarising its mechanism and synthetic applications.[102]

Some of the most important photochemical reactions of carbonyl and thiocarbonyl compounds are photocyclisations via intramolecular H-transfer.[103] This leads to cyclic compounds from more readily available acyclic precursors, such as the formation of cyclobutanols via 1-4 biradicals, accompanied by cleavage (Scheme 36).

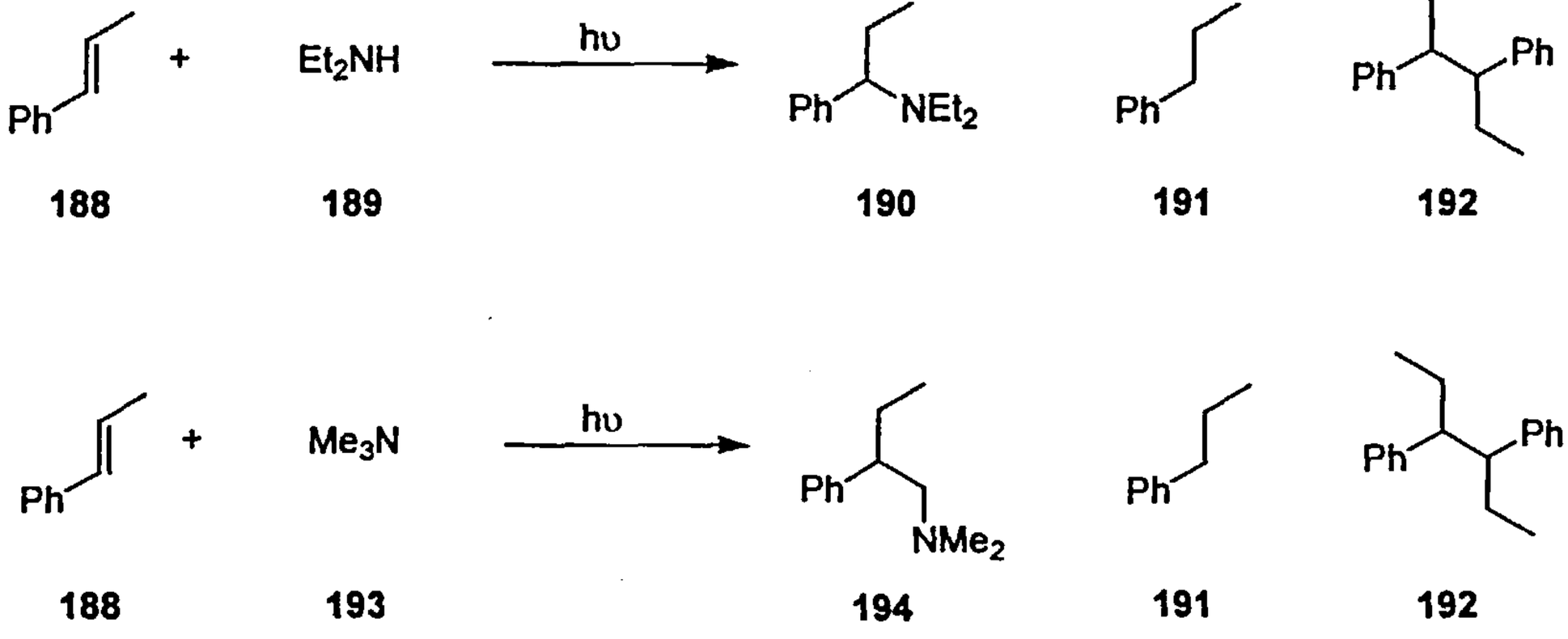


Scheme 36

Although some cyclic alkenes are known to undergo similar photochemistry to that observed in carbonyl compounds,[104] photochemical hydrogen abstraction by acyclic alkenes is less common. This is mainly attributed to competitive *E/Z* isomerisation processes. On the other hand, some acyclic alkenes such as stilbene and styrene have

been observed to undergo efficient hydrogen abstraction from electron donors such as amines.

The intermolecular photochemical addition reactions of secondary and tertiary aliphatic amines to styrene and its α and β alkyl derivatives was first reported over three decades ago by Cookson.[105] Tertiary amines were found to produce C-H adducts while secondary amines proceeded with N-H addition.[106] In both instances the addition was regioselective at the styrene α-carbon and the resulting amine adducts were accompanied by products of reduction and reductive dimerisation (Scheme 37).

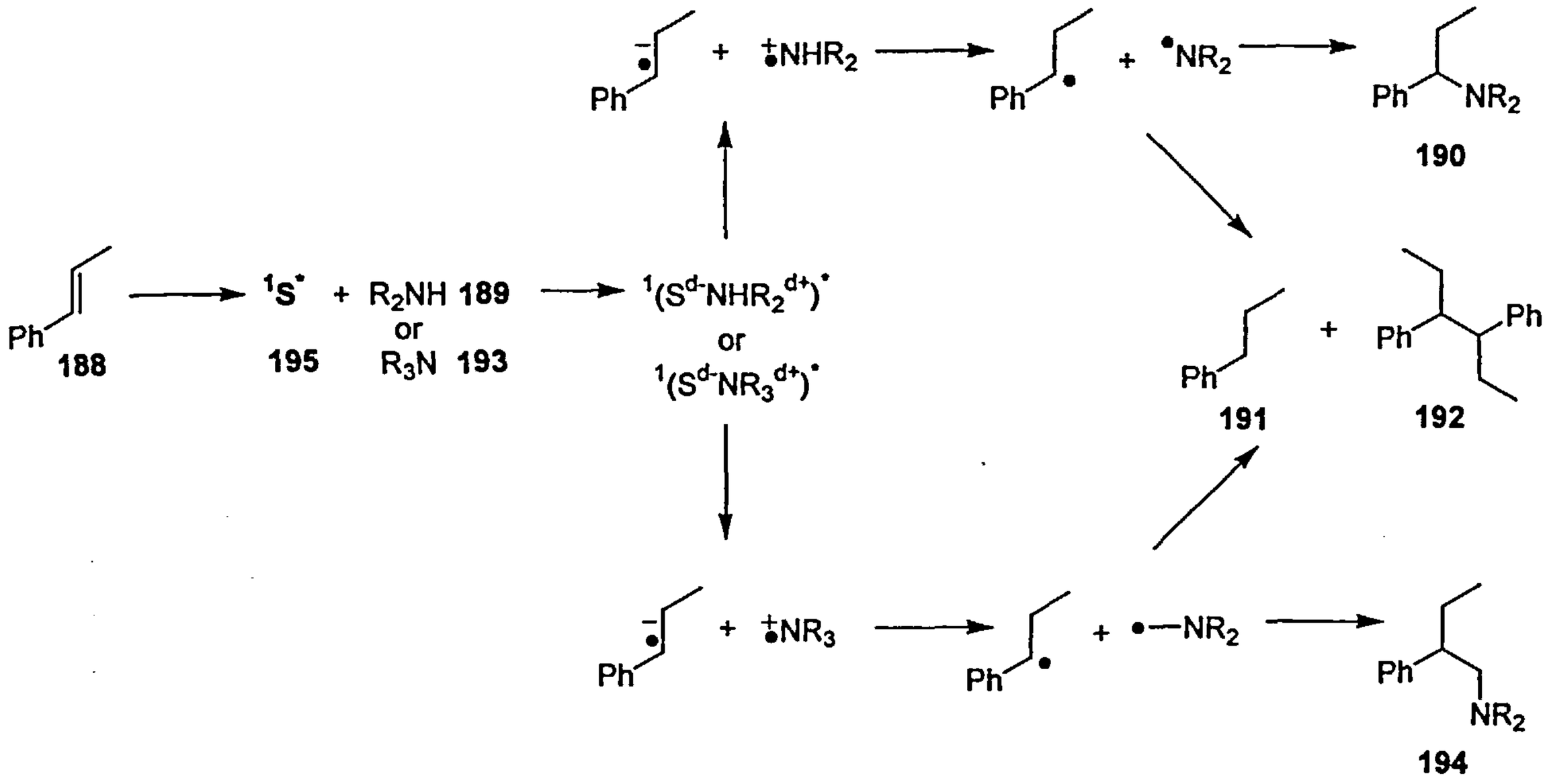


Scheme 37

The mechanism of photochemical addition has been the subject of numerous reports. Generally, light induces the transfer of an electron from a donor (D) to an acceptor (A) molecule, thus creating a radical cation and radical anion which can behave as synthons for an organic transformation.[107]

Equation 1

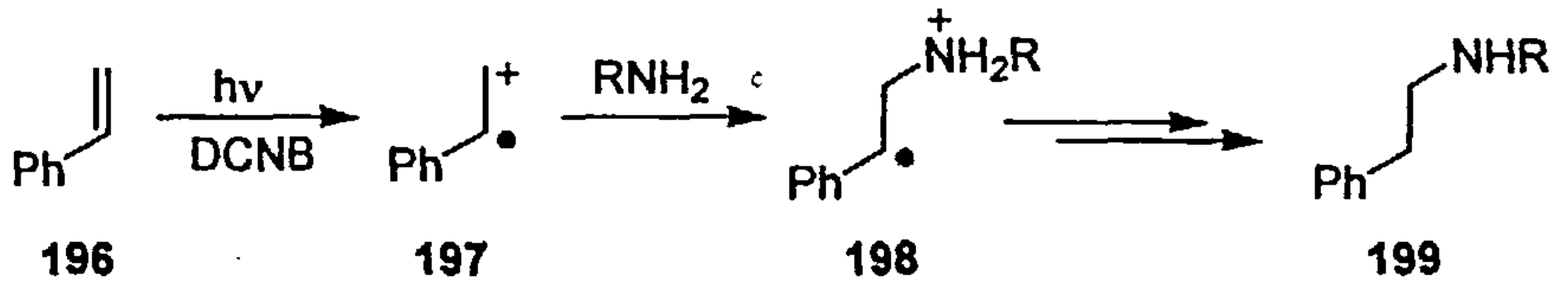
The mechanism in scheme 37 begins initially by irradiation of styrene to its excited singlet state, which is quenched by ground state amines **189** or **193** to form a charge transfer singlet exciplex. This can decay back to the ground state by emitting fluorescence or can undergo single electron transfer (SET) to form a radical ion pair. N-H transfer (secondary amines) or α-C-H transfer (tertiary amines) yields a pair of radicals that couple to form the observed adducts.[108]



Scheme 38

The polarity of the solvent governs the reactivity of the photochemical SET-generated ion radical and shows a marked difference between secondary and tertiary amines. Tertiary amines show an increase in product yields as the solvent polarity increases while the inverse is true for secondary amines.[106, 108] This is attributed to a greater degree of charge transfer character associated in the exciplexes of tertiary amines, compared to the relatively non-polar characteristics observed in secondary amines. Tertiary amine exciplexes also result in the formation of a fluorescent stilbene-amine exciplex while those of secondary amines do not. This is due to rapid N-H transfer resulting from N-H hydrogen bonding between the arene and secondary amine in nonpolar solvents. This provides a low energy pathway for the hydrogen transfer process, accounting for the absence of exiplex fluorescence.[109,110] The greater basicity of the β-carbon in the styrene anion radial compared to the α-carbon helps explain the observed regioselectivity, which leads to a stabilised benzyl radical.

In contrast quenching of excited singlet styrene derivatives by primary amines and ammonia does not result in addition products, presumably due to their higher oxidation potentials compared to secondary and tertiary amines.[106] However addition products are possible by a process of sensitisation.[111] The reaction path can be influenced by appropriate choice of an electron-transfer sensitiser, usually an electron acceptor such as dicyanobenzene (DCNB). Electron transfer from the styrene to DCBN produces the radical cation **197**, which is subject to nucleophilic attack by the primary amine. Reduction by $DCNB^{\bullet-}$ followed by hydrogen transfer produces the amine adduct **199** and regenerates the sensitiser (Scheme 39).

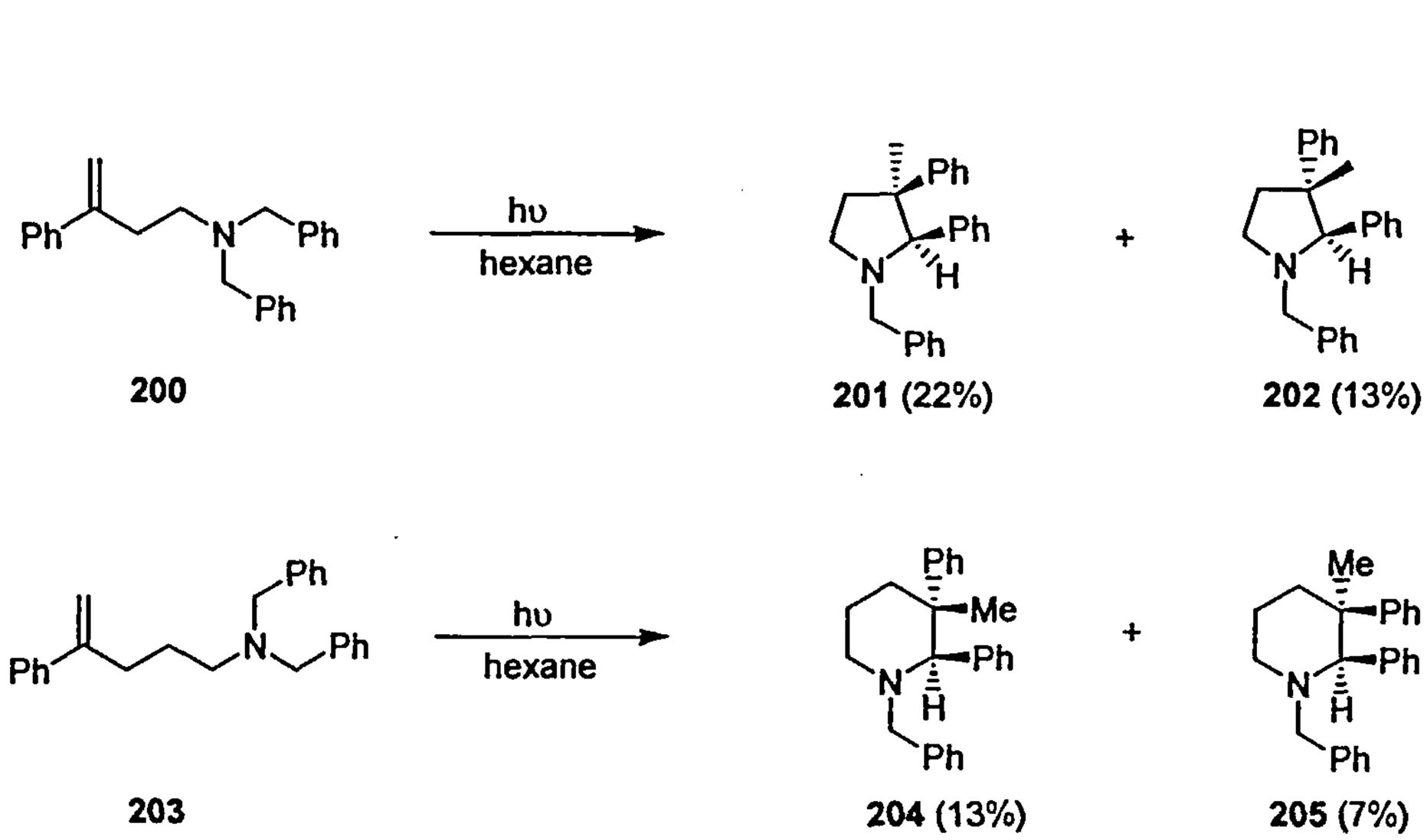


196 **197** **198** **199**

Scheme 39

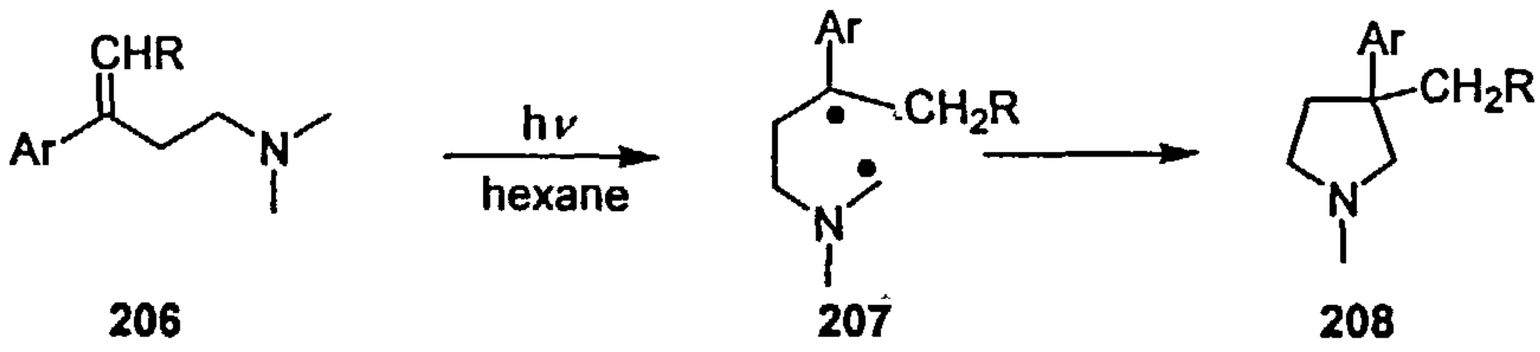
Intramolecular cycloaddition reactions either by direct or sensitised irradiation offers a versatile method for the synthesis of nitrogen heterocycles with a variety of ring sizes.[112] In these photochemical reactions the amine is tethered to the acceptor via an alkyl chain preventing both donor and acceptor from diffusing apart. Substrates such as α- or β-amino alkyl substituted styrenes have been shown to undergo far more efficient photochemical amine-styrene addition than found in intermolecular cases, offering promising synthetic application.[109]

Aoyama reported the first intramolecular photochemical cyclisation of amines with styrenes in 1985.[113] Irradiation of α-[(*N*,*N*-dibenzylamino)ethyl]styrene **200** with a low-pressure mercury lamp led to diastereomeric mixtures of *cis* and *trans* pyrrolidines **201** and **202** in 22% and 13% yields respectively. This was a result of 1,6-hydrogen transfer from the amine α-carbon to the β-position of the styrene and subsequent cyclisation of the resulting diradicals. Increasing the chain length to the propyl analogue **203** led to an unprecedented 1,7-hydrogen transfer, involving an eight membered transition state. The resulting *cis* and *trans* substituted piperidines **204** and **205** were isolated in 13% and 7% yield respectively. Since neither **200** or **203** were sensitizable nor quenchable they were found to be singlet reactions, both involving intramolecular charge-transfer exciplexes. Furthermore, compound **203** showed exciplex emission upon excitation, which could be of mechanistic interest. This is in contrast to compound **200**, which showed no exciplex emission, probably due to the exciplex of **200** being too short lived (Scheme 40).



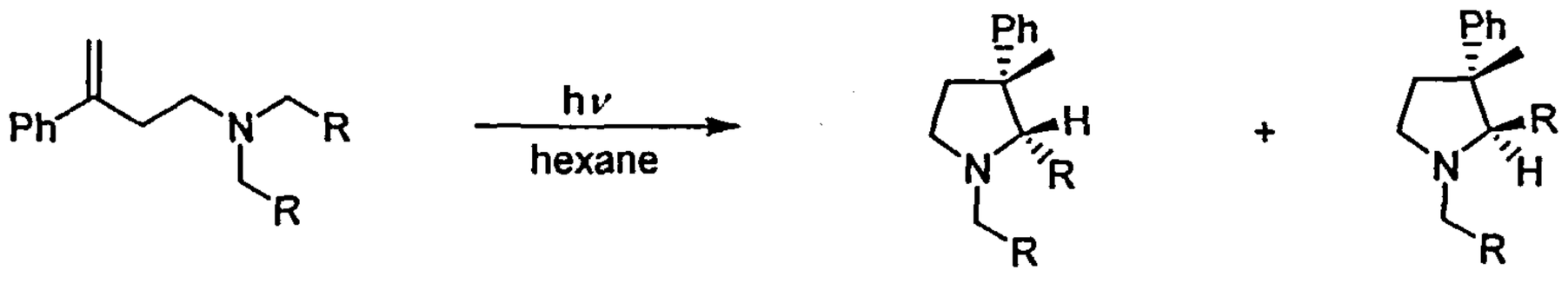
Scheme 40

Extension of this work towards the cyclisation of other α-[(*N*,*N*-dialkylamino)ethyl]styrenes led again to pyrrolidine products.[114] A 1,6-hydrogen abstraction by the terminal olefinic carbon and subsequent cyclisation of the diradical produced **208** in 78% yield from α-[(*N*,*N*-dimethylamino)ethyl]styrene **206**. Transforming to the 4-methoxy derivative **206b** resulted in an increase to 87%. However, substitution of the styrene double bond with a methyl group **206c** showed no marked affect on the yields of the cyclisation (Scheme 41).



206 **207** **208**

a: R=H, Ar=Ph — 78%
b: R=H, Ar=4-MeO-C_6H_6 — 87%
c: R=Me, Ar=Ph — 82%

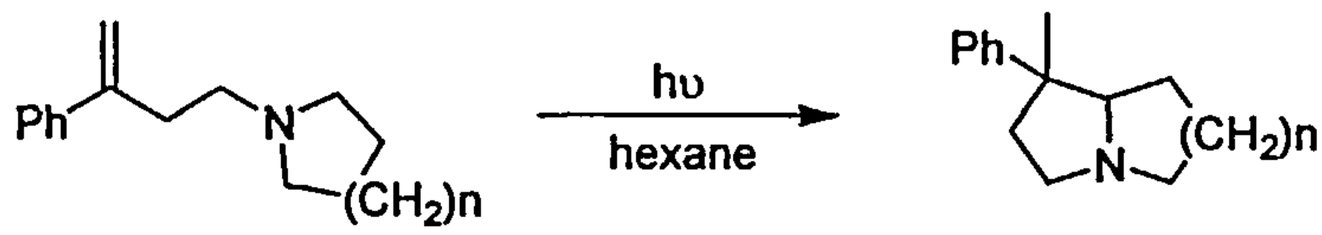


209: R=Me — ***cis*** **210** 36% — ***trans*** **211** 54%
200: R=Ph — **201** 28% — **202** 24%

Scheme 41

Changing the amine moiety to the diethyl derivative gave a mixture of the *cis* and *trans* isomers. As a result of improved experimental procedures to avoid product decomposition the yields of the previously reported cyclisation of α-[(*N*,*N*-dibenzylamino)ethyl]styrene **200** were also increased to 28% and 24% respectively.

Irradiation of cyclic amine **212a** resulted in the bicyclic compound **213a** in 73% yield. In the product, the phenyl group was found to be cis to the bridgehead methine hydrogen because of strong NOE observations upon irradiation. This stereoselectively has been explained in terms of syn C-H addition to the double bond[108] via a sterically favourable chair like transition state (Figure 6).



212 **213**

a: n=1 73%
b: n=2 84%

Scheme 42

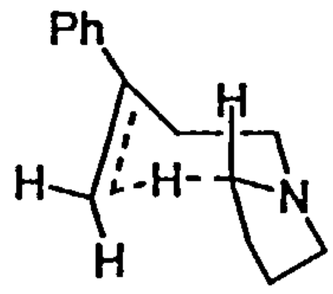
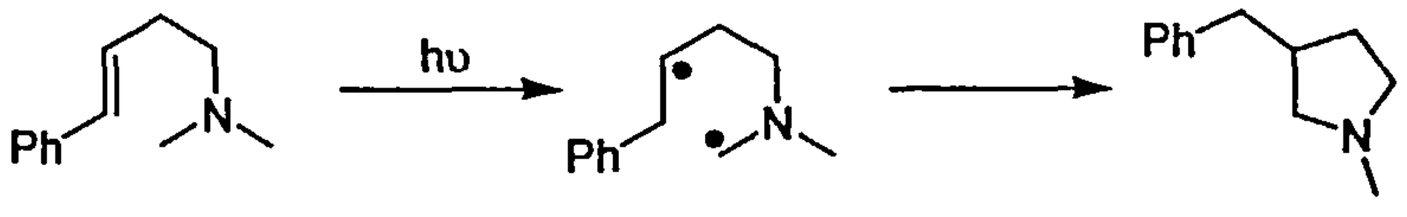


Figure 6

The observed photochemical behaviour of β-(aminoalkyl)styrenes, where the alkyl chain is attached at the β-carbon of the styrene, showed analogous results to that of the α-(aminoalkyl)styrenes.[115] For example, β-[(*N*,*N*-dimethylamino)ethyl]styrene **214** undergoes a 1,6-hydrogen transfer to yield this time the secondary radical **215** rather than the benzyl radical. The preference for the secondary radical in some cases as opposed to the more stable benzyl radical is not clear. It might be attributed to maximising orbital overlap to allow for the hydrogen abstraction step to occur via a least motion pathway. Lewis has demonstrated that the regiochemistry, efficiency and

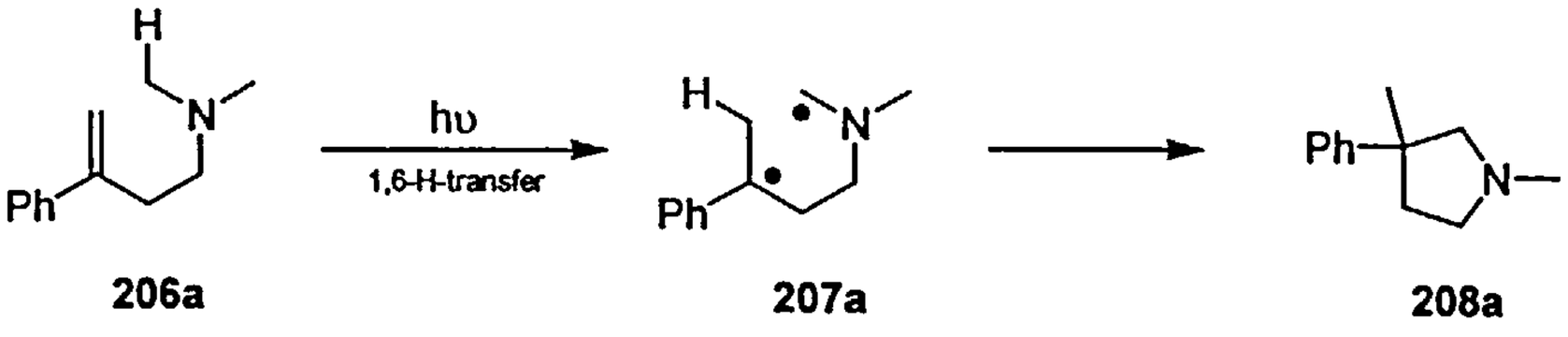
product yields are dependent on the length of the polymethylene chain, the point of attachment (α vs β) and the solvent polarity (Scheme 43).[109]



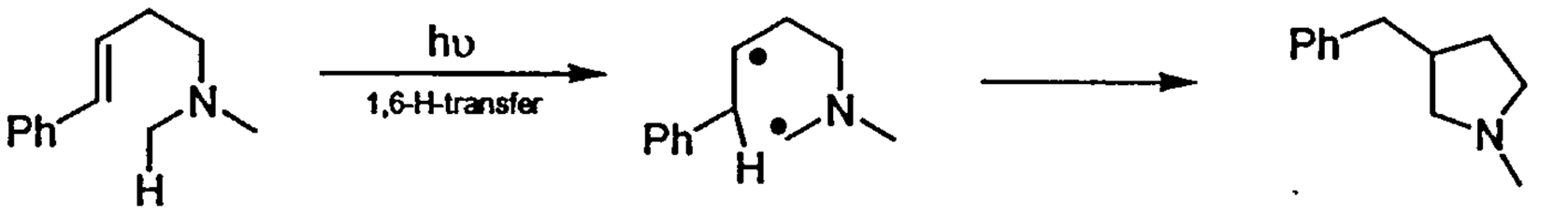
214 **215** **216**

Scheme 43

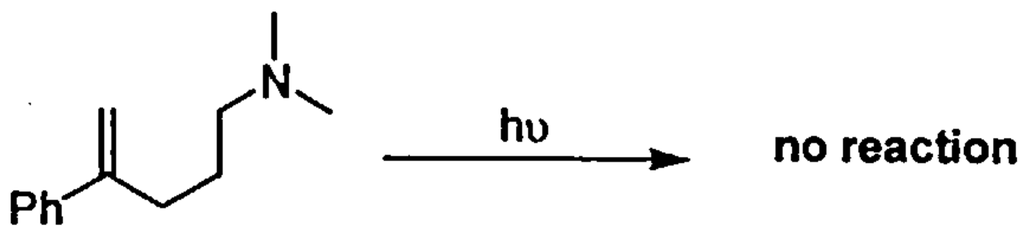
Lewis investigated the photochemical behaviour of both α and β-(*N*,*N*-dimethylamino)alkyl styrenes in which the aminoalkyl group is attached to the styrene α or β-carbon by either a ethyl, propyl or butyl chain.[115] He found that only those compounds containing an ethyl or butyl chain displayed intramolecular addition products. The (aminopropyl)styrene exciplexes of **217** and **218** remained unreactive even though a number of pathways for H-transfer, such as 1,5-H transfer for **217** and 1,6-H transfer for **218** can be envisaged. As previously discussed both the α and β-(*N*,*N*-dimethylamino)ethyl styrenes **206a** and **214** undergo photochemical addition which leads to the formation of pyrrolidine heterocycles **208a** and **216** as single products respectively. By contrast the α-(*N*,*N*-dimethylamino)butyl styrene **219** reacts via the intermediacy of a 1,5-biradical resulting from 1,6-H transfer from the *N*-methylene to the styrene β-carbon to yield a diastereomeric mixture of cyclopentanes **221** and **222** in a 4:1 ratio. Alternatively β-(*N*,*N*-dimethylamino)butyl styrene **223** reacts via 1,5-H transfer from N-methylene to the styrene β-carbon resulting in a 1,6-biradical that cyclises to form a diastereomeric mixture of *cis* and *trans* substituted cyclohexanes **225** and **226** in an 8:1 ratio (Scheme 44).



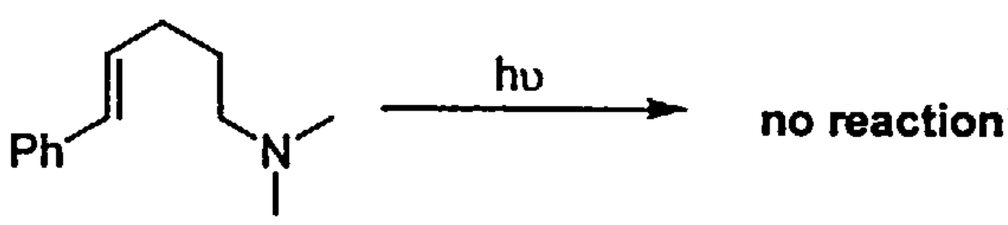
206a **207a** **208a**



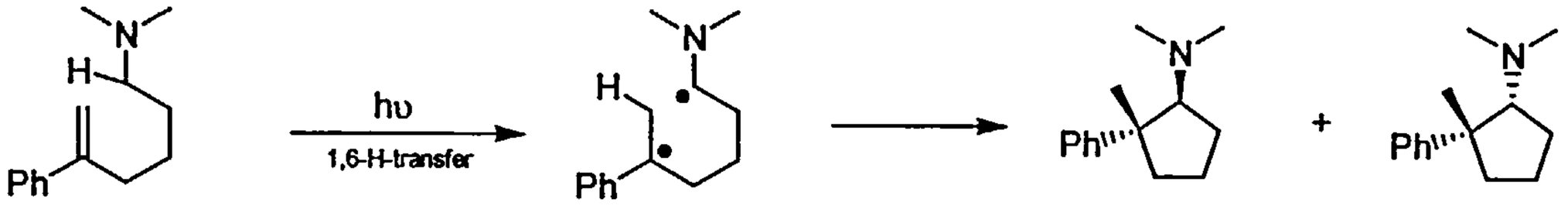
214 **215** **216**



217

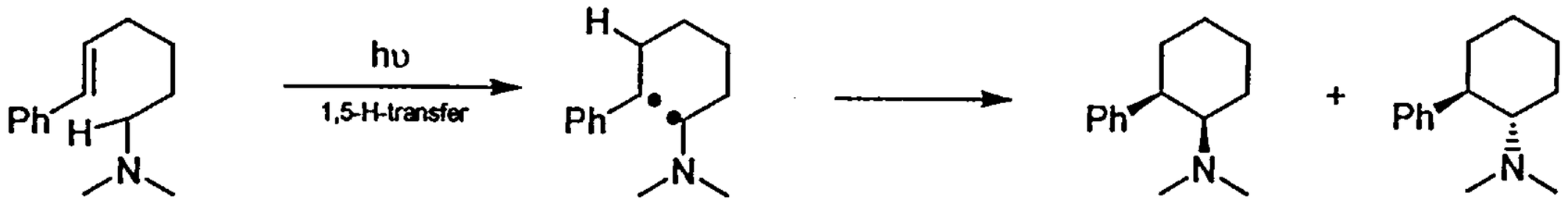


218



219 **220** **221** **222**

4:1



223 **224** **225** **226**

8:1

Scheme 44

The failure of the (aminopropyl)styrenes **217** and **218** to form intramolecular adducts is surprising, especially when it was observed they formed longer lived fluorescent exciplexes compared to their ethyl or butyl analogues in hexane solution (Scheme 44).[109, 115] This indicates that the absence of adduct formation is probably a consequence of poor proton transfer and not inefficient exciplex formation or as a result of rapid exciplex decay.

Extensive studies carried out by De Schryver and Van der Auweraer[116] suggest that in non-polar solvents the arene-trialkylamine exciplexes adopt specific folded conformations. This maximises orbital overlap and columbic attraction whilst minimising steric interactions of the alkyl chain.

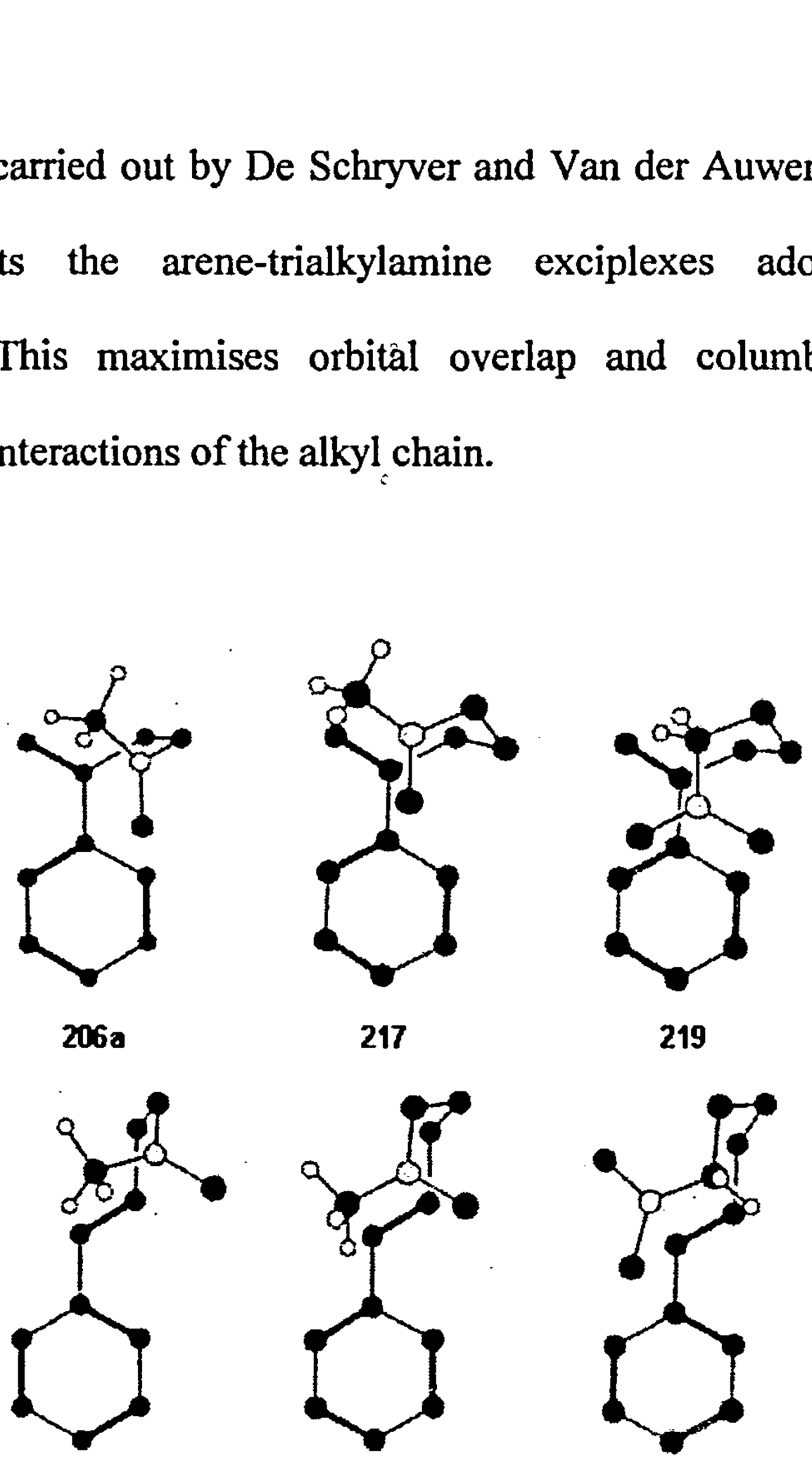


Figure 2

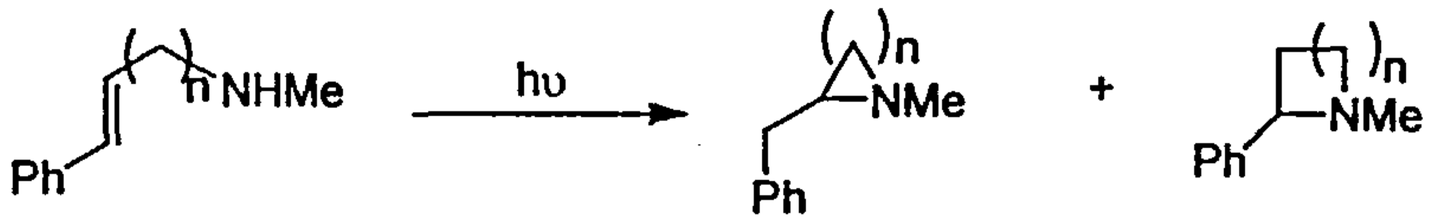
The fluorescent [(*N*,*N*-dimethylamino)ethyl]arenes are proposed to adopt a conformation that places the nitrogen above the arene plane near the ipso carbon. Analogous conformations on the exciplexes of α and β-[(*N*,*N*-dimethylamino)ethyl]styrenes **206a** and **214** place the *N*-methyl hydrogen above the β-carbon of the styrene in the exciplex of **206a** and above the α-carbon in the exciplex of **214**. Similarly, the [(*N*,*N*-dimethylamino)butyl]styrenes **219** and **223** were shown to adopt conformations in which the nitrogen lies near the centre of the aromatic ring. This places a N-methylene hydrogen above the β-carbon in both **219** and **223**. Least motion proton transfer forms the biradical intermediates, which lead to the observed products. The failure of α and β-[(*N*,*N*-dimethylamino)propyl]styrenes **217** and **218** to undergo cyclisation has been explained due to the folded conformations **217** and **218** which places the nitrogen above the plane of the arene beyond the ipso carbon. This conformation orientates the *N*-methyl hydrogens away from the styrene double bond, beyond the styrene β-carbon in **217** and α-carbon in **218**. The absence of a least motion pathway for 1,7-H transfer as seen in [(*N*,*N*-dibenzylamino)propyl]styrene **203** is probably a consequence of the lack of reactivity observed for these compounds, which is supported by the observed longer exciplex decay times compared to its ethyl and butyl analogues (Scheme 44).

In contrast to the intermolecular additions of tertiary amines to styrenes, intramolecular photoaddition reactions are highly dependent on the nature of the solvent. Product formation is only observed in solvents less polar than tetrahydrofuran and the quantum yields decrease markedly with an increase in solvent polarity.[109] This decrease is due to a change in the conformation of the exciplex from compact in hexane to more looser

exciplex geometry in more polar solvents such as diethyl ether. Polar solvents are proposed to stabilise the exciplex and as a result, the proton transfer pathways becomes less energetically favourable. This increase in activation energy for proton transfer means that the formation of the biradical becomes too slow to compete with the decay process, resulting in ground state reactants and low quantum yields.

In comparison to the behaviour of tertiary(aminoalkylstyrenes), the intramolecular photoadditions of secondary amino analogues display much lower degrees of dependence on the length of the chain, regioselectivity of proton transfer and nature of the solvent. Intramolecular additions of secondary amines occur via exclusive N-H addition. The absence of either exciplex fluorescence or selective quenching suggests that this might be a consequence of lower activation energy associated with N-H transfer compared to C-H transfer.

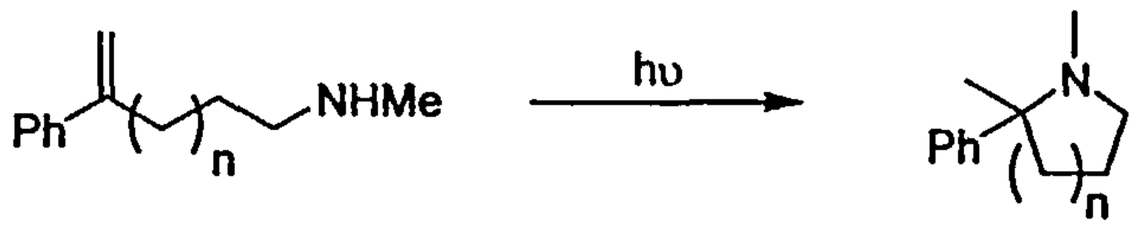
β-[(*N*-methylamino)alkyl]styrenes with one to five methylenes separating the styrene and amine yield a mixture of regioisomeric adducts in which the C-N bond formations occurs at either the β- or α-carbon. The addition product at the benzylic carbon is the major product for when n=3 and predominates in cases where n=1, 2, or 5. When n=4 intramolecular addition occurs mainly at the β-carbon in the ratio 7:1 in MeCN. It is presumed that the chain length is too short to allow proton transfer at the α-carbon when n=1 and 2. When the alkyl chain is longer as in n=5, the intramolecular exciplex is thought to permit similar behaviour to that seen in intermolecular cases (Scheme 45).[117]



227a: n=1 **228a** **229a**
227b: n=2 **228b** **229b**
227c: n=3 **228c** **229c**
227d: n=4 **228d** **229d**
227e: n=5 **228e** **229e**

Scheme 45

Aoyama has demonstrated that intramolecular addition of α-aminopropyl and α-aminobutyl styrenes form a single adduct in which nitrogen is bonded to the benzylic carbon.[112, 113, 114] The reaction proceeds with very high regioselectivity, forming pyrrolidine **231a** and piperidine **231b** adducts in good preparative yields (80% and 75% respectively) (Scheme 46).

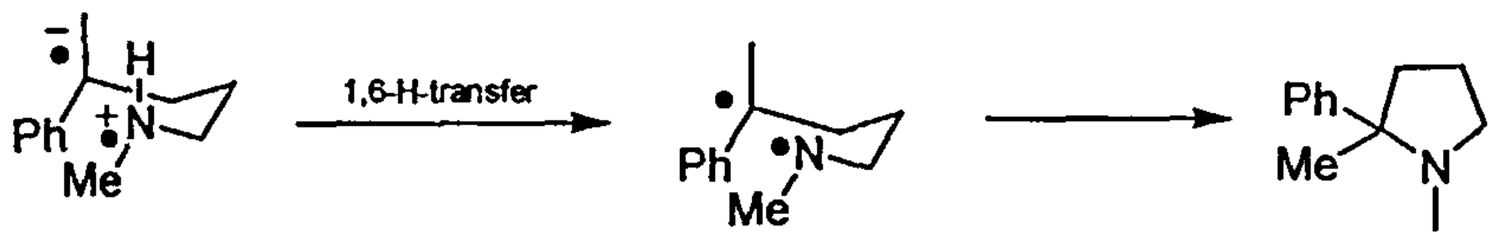


230a: n=1
230b: n=2

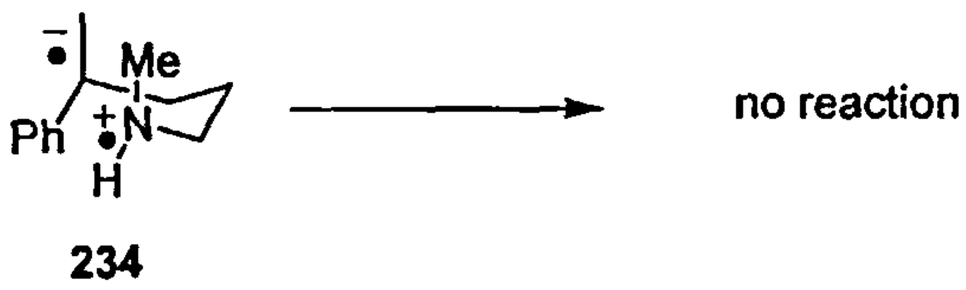
231a: n=1
231b: n=2

Scheme 46

Inspection of the low energy folded exciplex conformation **230a** can be explained by N-H transfer from the pseudo-axial position to the styrene terminal carbon helps explain the observed regiochemistry. The absence of any products arising from intramolecular addition of nitrogen at the β-carbon is due to an unfavourable pathway for N-H transfer to the styrene α-carbon as depicted in scheme 47.



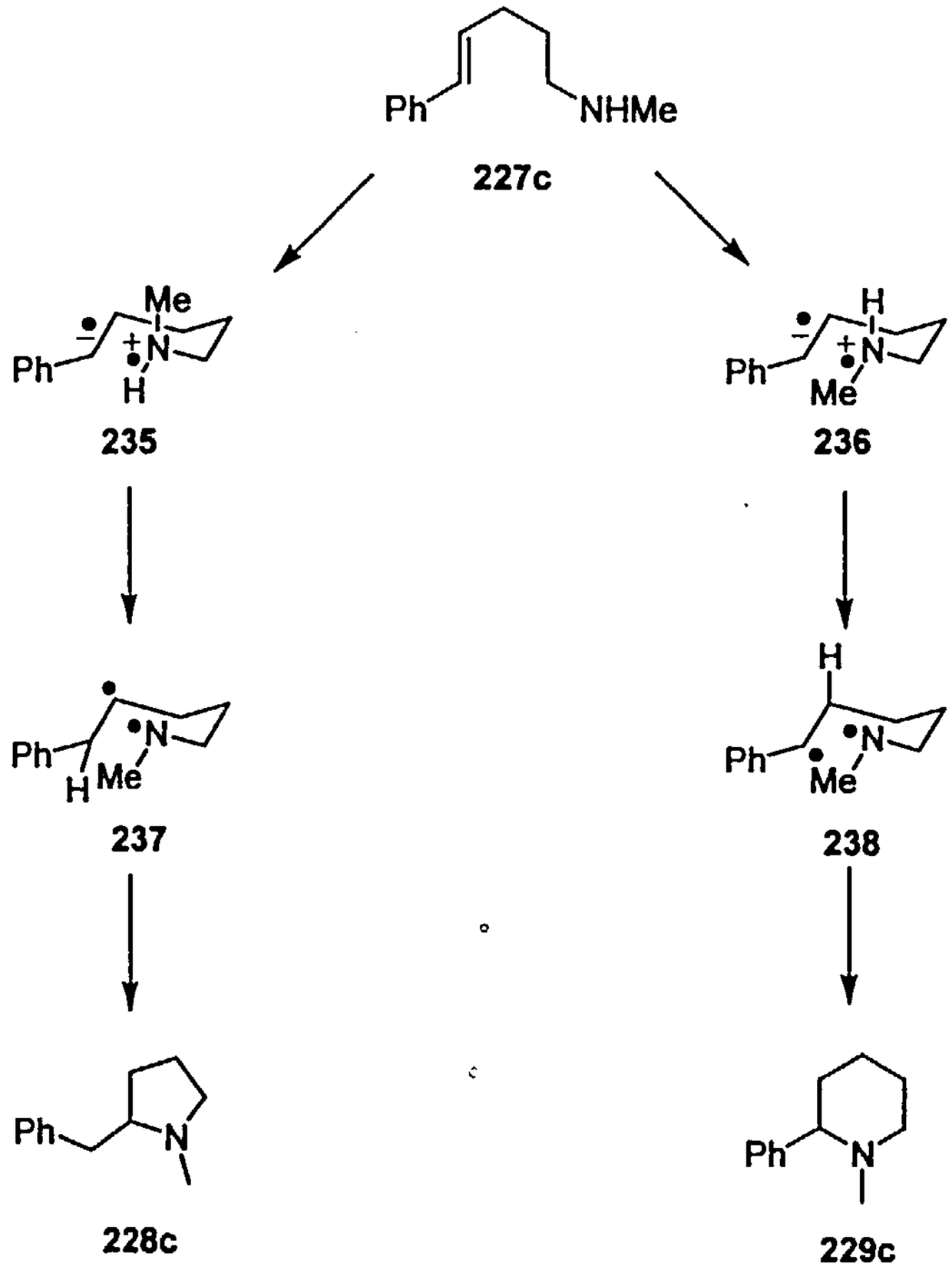
230a **232** **233**



234

Scheme 47

Intramolecular addition reactions for both α- and β-[(*N*-methylamino)propyl]styrene **230a** and **227c** is surprising, especially because irradiation of their tertiary analogues α- and β-[(*N*,*N*-dimethylamino)propyl]styrenes **217** and **218** resulted in no reaction (Scheme 44). The two adducts **228c** and **229c** that result from irradiation of β-[(*N*-methylamino)propyl]styrene **227c** are proposed to be formed from the folded exciplex conformations **235** and **236**, which undergoes proton transfer to the α- or β-carbon from the N-H that is either equatorial or axial. The lowest energy conformation **236**, which places the methyl group in the pseudo-equatorial position produces the piperidine **229c** as the major product (Scheme 48).



Scheme 48

Unlike tertiary aminoalkyl styrenes, secondary aminoalkyl styrenes show only slight dependence on the solvent polarity during cycloadditions and show comparable efficiency in both polar and non-polar solvents.[109] The absence of solvents to significantly induce change in the exciplex is mainly attributed to intramolecular hydrogen bonding between the amine N-H and styrene. This prevents the exciplex from adopting more looser or extended configurations, a primary factor responsible for the lack of reactivity in tertiary aminoalkyl derivatives.

Irradiation of aminoalkyl styrenes and other aryl-olefins is a potentially powerful and attractive method for the synthesis of heterocyclic rings of differing ring size. However, its use in the atom-economic synthesis of enantiomerically pure target molecules has been limited.[118] To date there has been no application of this methodology towards a photomediated asymmetric synthesis of natural products.

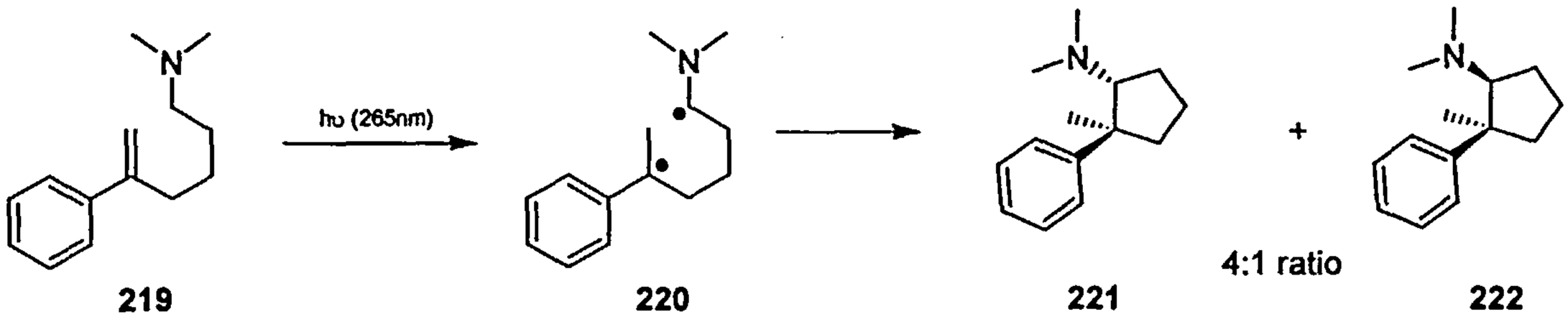
Chapter 2

Results and Discussion

2.1 Aim of the project

It was our intention to develop a fundamentally new approach to the asymmetric synthesis of cuparene **1** and herbertane **2** class of sesquiterpenoids based on a concept of "asymmetric photochemistry" a potentially powerful yet virtually unexplored area in modern asymmetric synthesis.

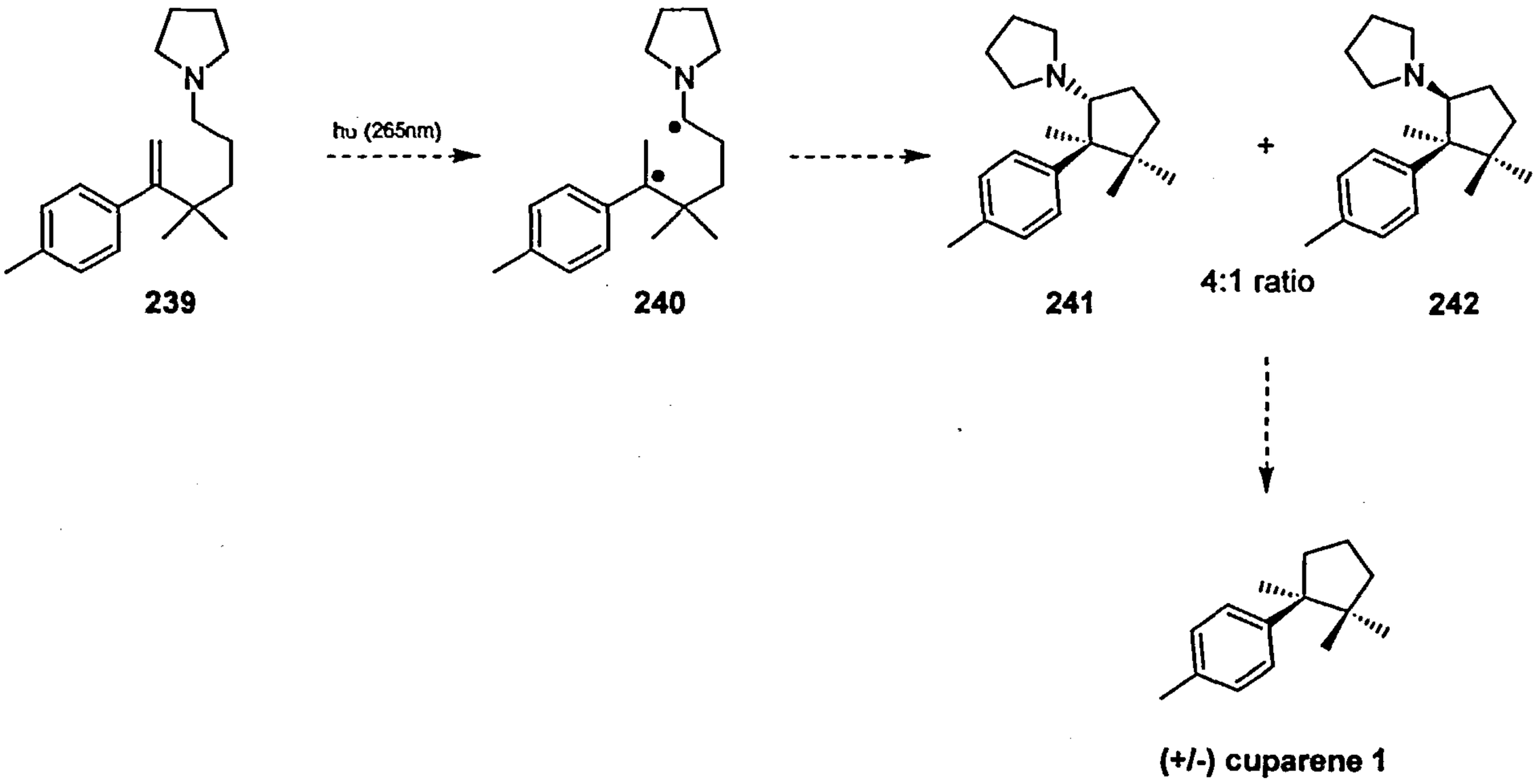
This approach to cuparene is based upon the photomediated ring closure of α-(dimethylaminobutyl)styrene **219** to cyclopentane adducts **221** and **222** reported by Lewis (Scheme 44).[115] The reaction is proposed to proceed via electron transfer from the ground state amine to the excited singlet state of the styrene, followed by a 1,6-hydrogen transfer to generate the 1,5-biradical **220**. Cyclisation of the resulting diradical provides a 4:1 ratio of cyclopentane adducts **221** and **222** respectively.



219 **220** **221** **222**

Scheme 49

The Lewis cyclisation could be applied to a synthesis of the cuparene skeleton if such a reaction can tolerate substitution in the aromatic ring and connecting chain. Providing the cyclisation is successful, removal of the amine moiety via a deamination process should then furnish the natural product.

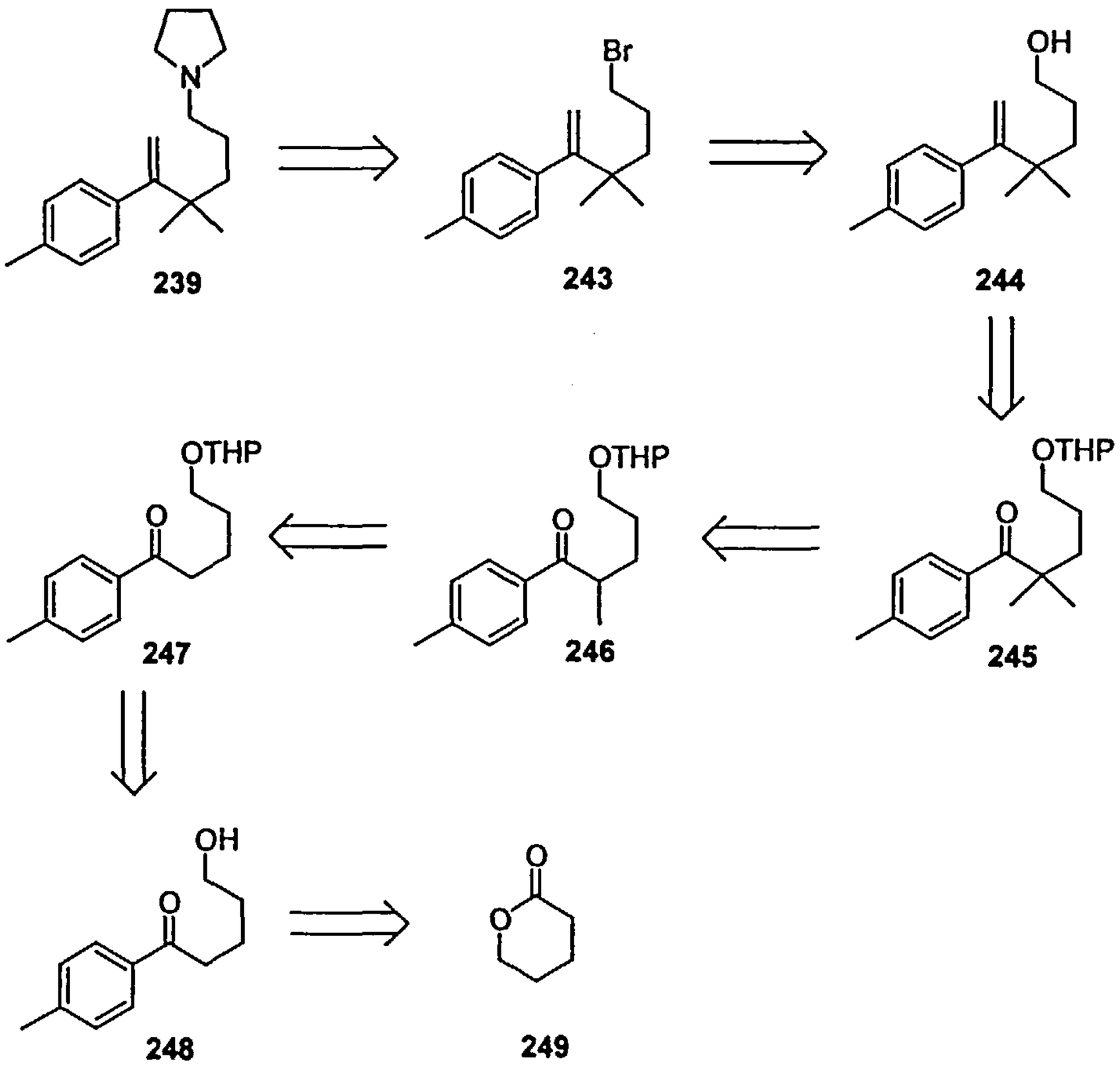


Scheme 50

Furthermore, the possibility of employing both C_2-symmetric and non C_2-symmetric chiral amine auxiliaries in place of dimethylamine could offer a means to control the absolute configuration at the new stereocentre and hence lead to an asymmetric synthesis of the natural product.

2.2.1 Retrosynthetic analysis I

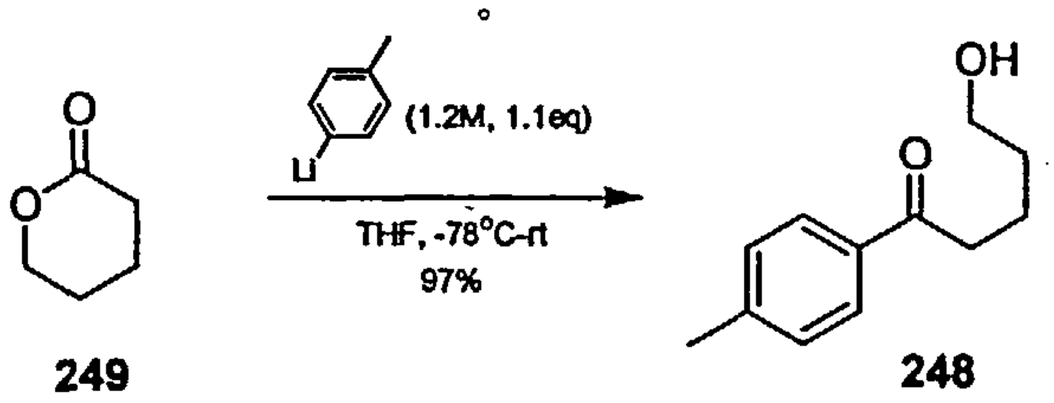
In order to test this hypothesis, initial efforts were directed towards the cyclisation of key intermediate **239**, which would assemble the core cuparene skeleton. A search in the literature showed that the requisite alkyl bromide **243** could be prepared by a similar synthesis to that reported by Bailey.[119] Mesylation of alcohol **244** followed by conversion to the bromide should permit the formation of **243**. Wittig reaction on the protected ketone followed by deprotection furnishes the alcohol **244**. Compound **245** could be prepared from the protected ketone **247** via sequential generation of the enolate followed by quenching with methyl iodide. Ketone **247** can be made from ring-opening of commercially available δ-valerolactone°**249** followed by THP protection.



Scheme 51

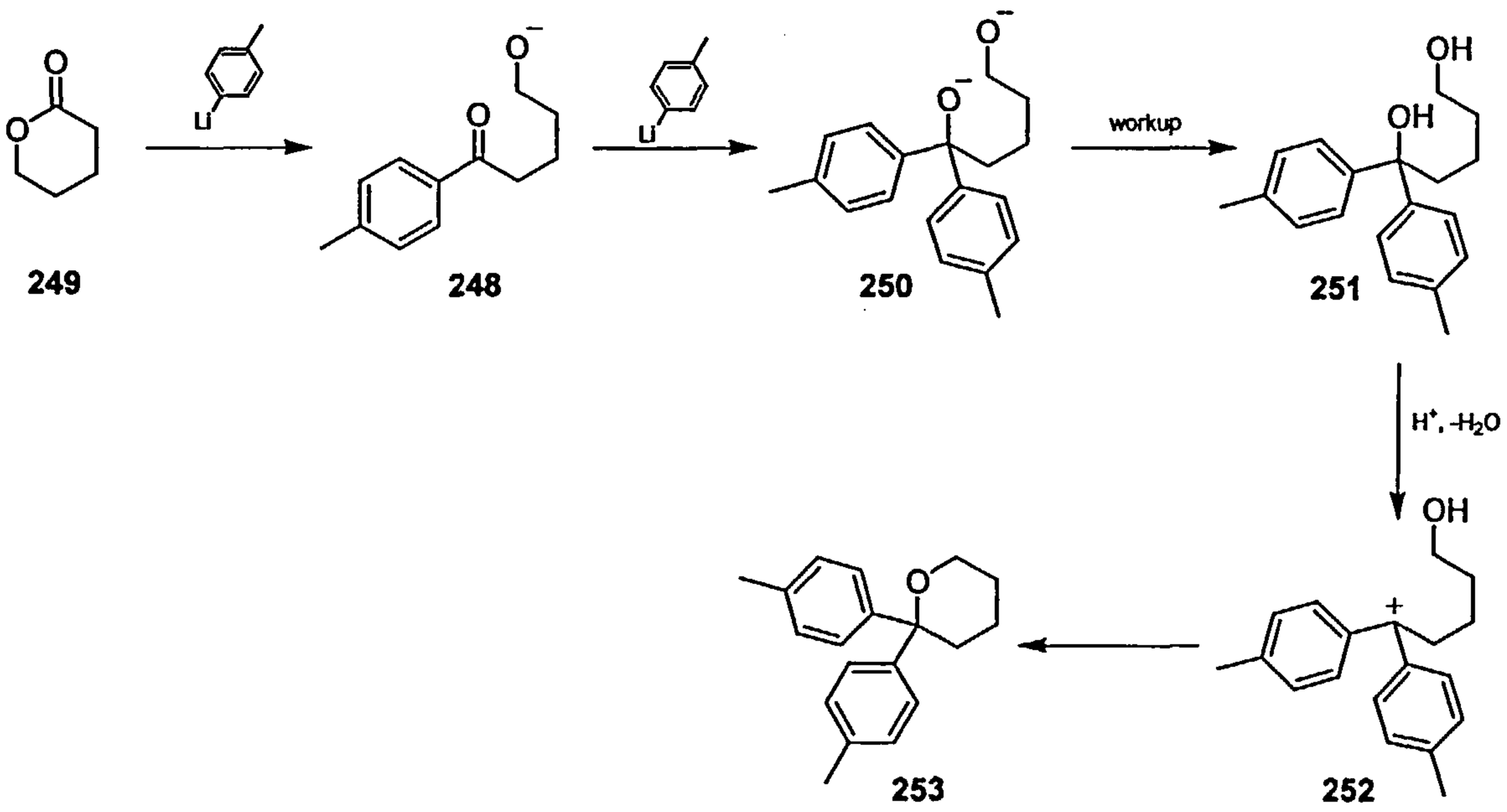
Synthesis of 5-Hydroxy-1-(4-methylphenyl)-1-pentanone (248).

Nucleophilic ring opening of δ-valerolactone **249** with *p*-tolyllithium was carried out without incident and resulted in yields exceeding those reported in the literature (lit. 90%).[120] The organolithium reagent was prepared as a 1.2M solution in ether from *p*-bromotoluene and lithium shavings. Preliminary work revealed that the product yields decreased when an excess of the organolithium was used. This decrease in yield is due to the formation of a di-*p*-tolyl-tetrahydropyran **253** by-product, which presumably is formed from second nucleophilic attack of the organolithium to the initially formed ketone **248** as indicated in scheme 53.



249 **248**

Scheme 52

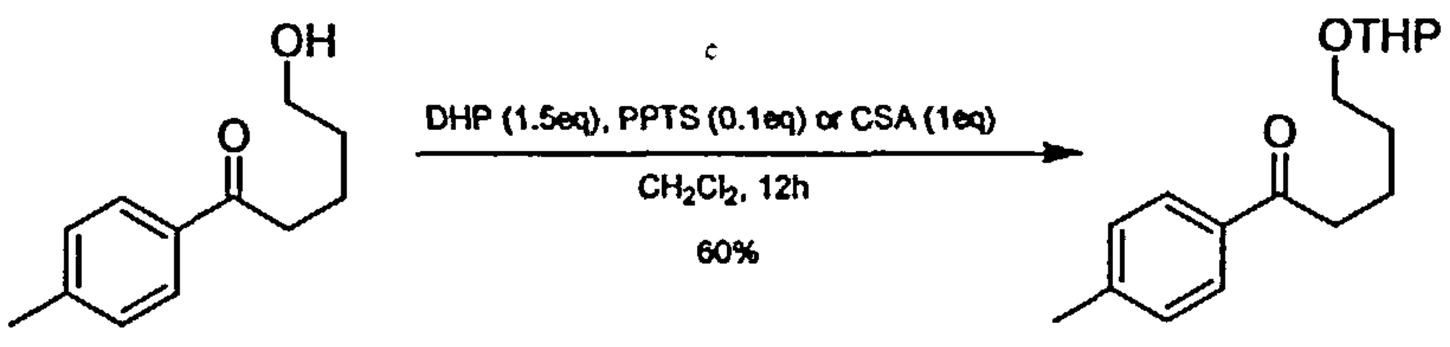


249 **248** **250** **251** **252** **253**

Scheme 53

Synthesis of 5-[(Tetrahydropyranyl)oxy]-1-(4-methylphenyl)-1-pentanone (247).

In order to introduce the *gem*-dimethyl group, the alcohol functionality was first protected as its tetrahydropyranyl (THP) derivative. The yield was slightly lower than that reported in the literature (lit.; 78%) and attempts to increase the yield by using camphorsulfonic acid (CSA) rather than the precedented pyridinium-*p*-toluenesulfonate resulted in only a slight increase (60% to 63%). However, this was sufficient for our purposes and no further attempts to optimise the yield were made. The desired THP-ether **247** was purified by column chromatography and matched all spectroscopic data (Scheme 54).[119]

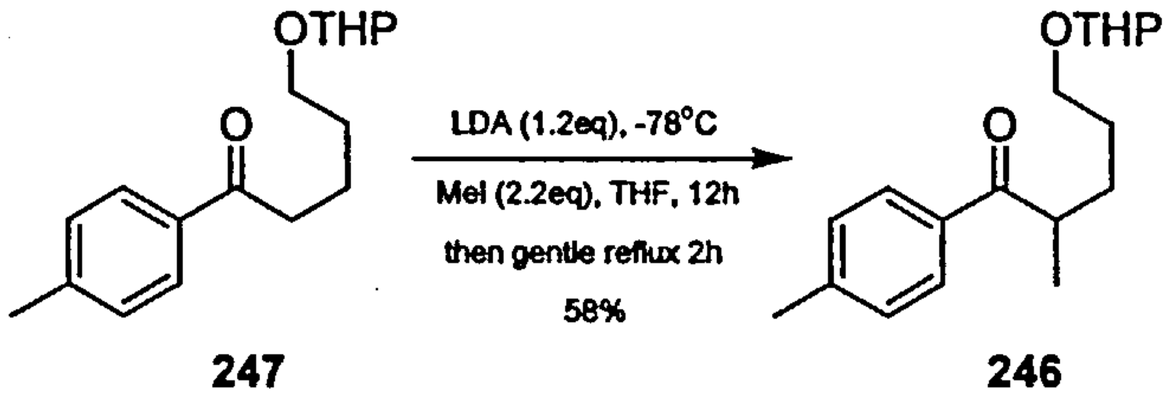


248 **247**

Scheme 54

Synthesis of 5-[(Tetrahydropyranyl)oxy]-2-methyl-1-(4-methylphenyl)-1-pentanone (246).

The conversion of **247** to the α-methylated product **246** was achieved without any major complications. Deprotonation at the α-position using LDA at -78°C generates the lithium enolate which is quenched by the electrophile iodomethane. The product was purified by column chromatography and had data consistent with that reported (Scheme 55).[119]



247 **246**

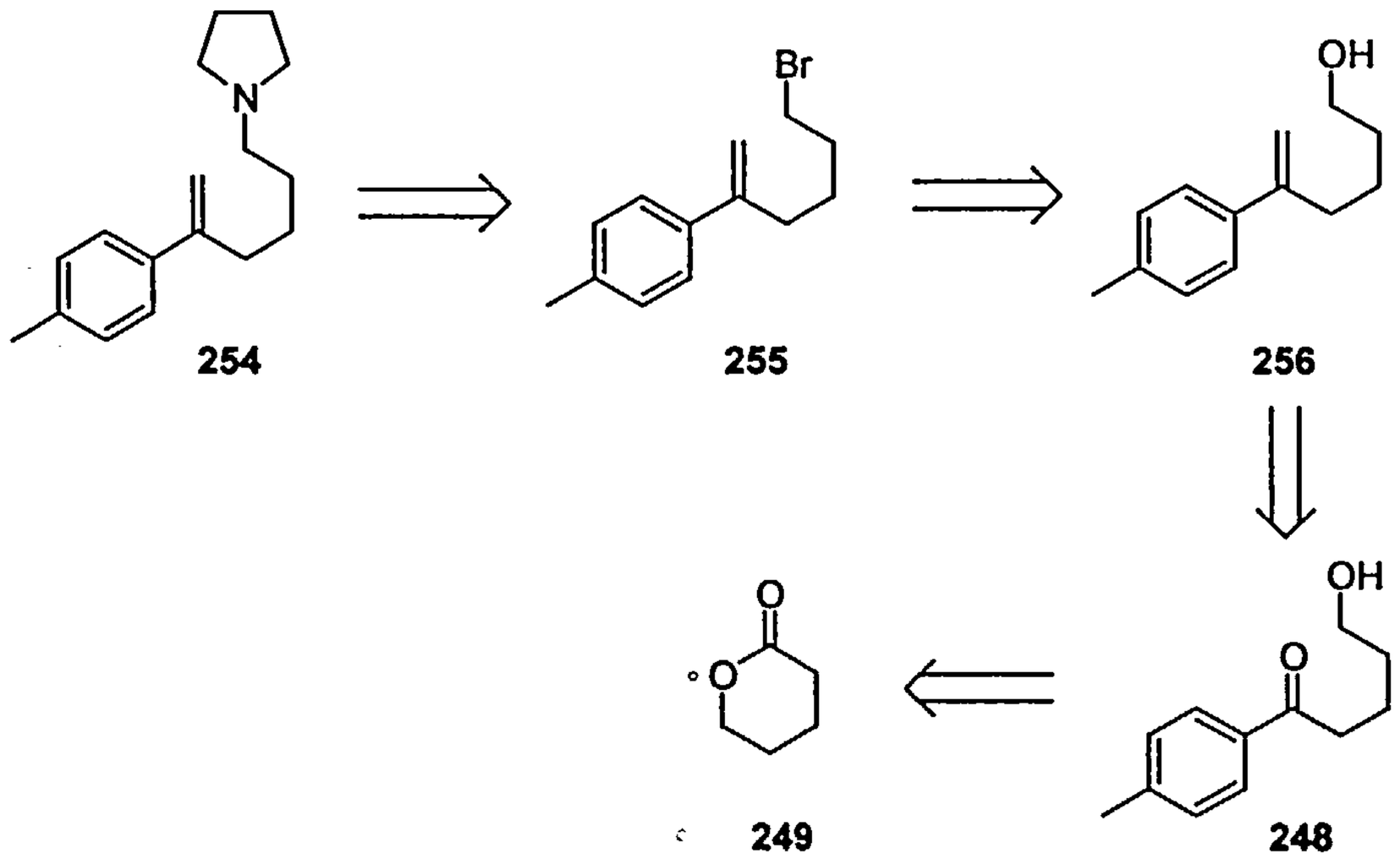
Synthesis of 5-[(Tetrahydropyranyl)oxy]-2,2-dimethyl-1-(4-methylphenyl)-1-pentanone (245).

The second alkylation step proved to be problematic resulting at best in inseparable mixtures of **245** and **246**. A number of different bases and conditions were employed in an attempt to generate the enolate, without success (Table 1).

Table 1: Conditions employed for second alkylation.

Conditions	Result
KHMDS (1.3eq), -78°C-rt, MeI (2.2eq), 18h	Inseparable mixture of **245** and **246**
LiHMDS (1.05eq), -78°C-rt, MeI (2.2eq), 18h	recovery of starting material **246**
KHMDS (0.5M,1.5eq), -78°C-rt, MeI (2.2eq), 18h	Inseparable mixture of **245** and **246**
LDA (2.4eq), -78°C-rt, MeI (4.4eq), 18h (one pot on compound **247**)	**246**
NaH (2.5eq), DMF, rt, MeI (2.2eq), 24h	recovery of starting material **246**
KHMDS (2eq), -78°C-rt, MeI (3eq)/DMPU (3eq), 18h	intractable mixture

In light of this result, the above route was abandoned and it seemed more prudent to initially investigate the cyclisation without the geminal-dimethyl group in place (Scheme 56).

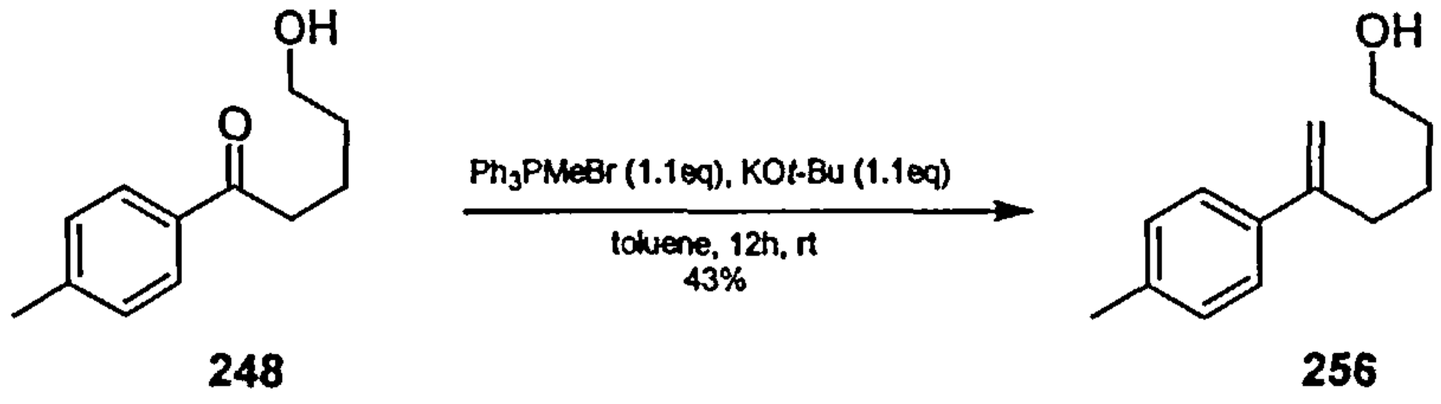


254 **255** **256** **249** **248**

Scheme 56

Synthesis of 5-*p*-tolyl-hex-5-en-1-ol (256).

With compound **248** already synthesised, it seemed reasonable to conduct a Wittig reaction on alcohol **248**. The conversion to the alkene **256** was achieved in moderate yield (43%) employing a phosphorous ylide, which was produced by deprotonation of the alkyl phosphonium salt using potassium *tert*-butoxide. Alternative strong bases such as LDA, *n*-butyllithium and potassium hexamethyldisilazide were also employed, but showed no marked difference in the yield. The resulting alkene **256** was purified by flash column chromatography and displayed identical spectroscopic data to that reported in the literature (Scheme 57).[119,121]

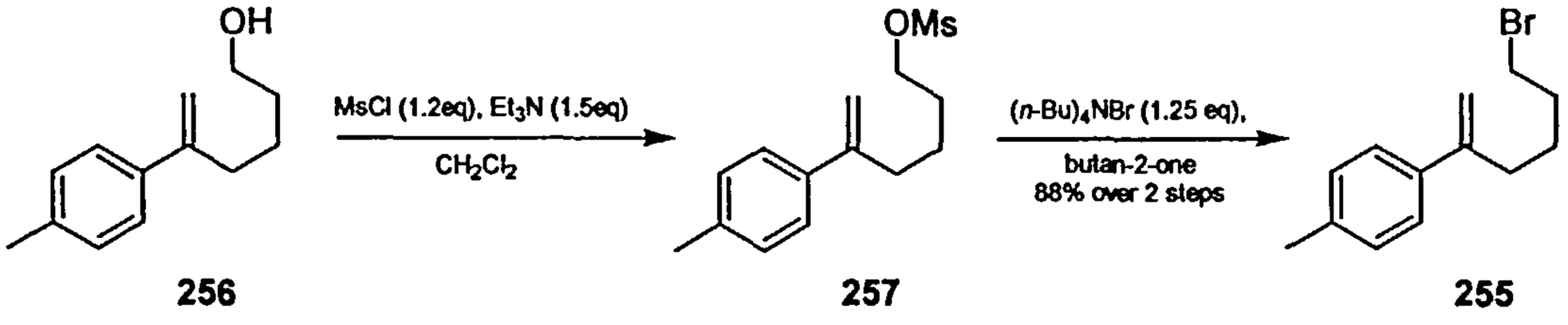


248 256

Scheme 57

Synthesis of 1-[1-(4-Bromobutyl)-vinyl]-4-methylbenzene (255).

A number of different procedures are available for the conversion of alcohols to halides.[122] Initially a one step conversion to the corresponding bromide was examined.[123] This utilised triphenylphosphine dibromide as the key reagent, unfortunately this transformation was unsuccessful and produced only intractable mixtures. However, simple conversion to the mesylate employing a procedure by Crossland and Servis[124] followed by displacement with tetra-n-butyl ammonium bromide in butan-2-one gave the alkyl bromide in 88% yield over 2 steps (Scheme 58).



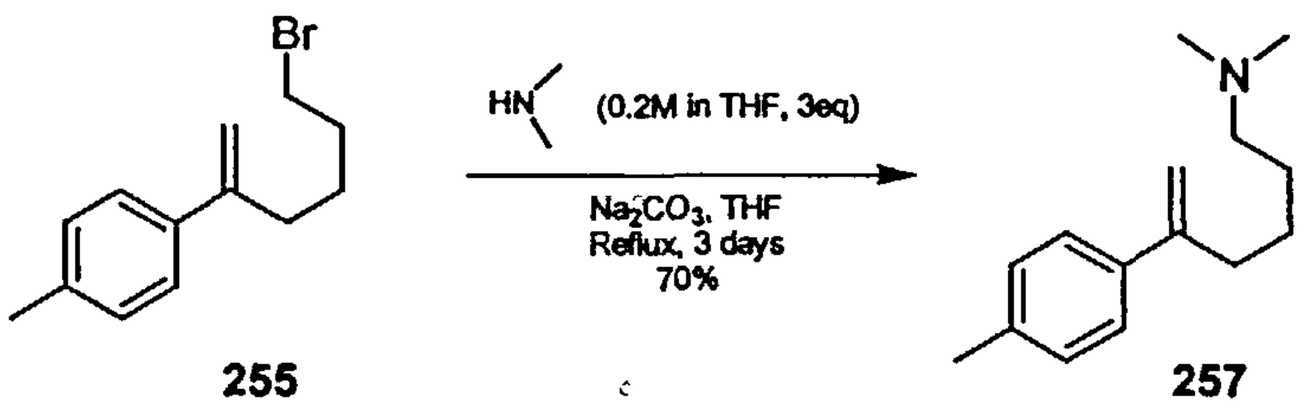
256 257 255

Scheme 58

The mechanism is well known and proceeds via nucleophilic addition of the alcohol onto the sulfene, derived from E_2 elimination of HCl from mesyl chloride.[124]

Synthesis of 1-(5-*p*-tolyl-hex-5-enyl)-pyrrolidine (254).

It was anticipated that coupling of the amine with alkyl bromide **255** would provide the required aminoalkyl styrene derivative to test the preliminary cyclisation. Early attempts began by refluxing excess dimethyl amine in the presence of triethylamine, but this resulted in mainly recovery of starting material. However, refluxing in the presence of sodium carbonate (10 eq) in ethanol over 2-3 days resulted in the formation of aminoalkyl styrenes **257** and **254** in 70% and 82% yields respectively.[125]



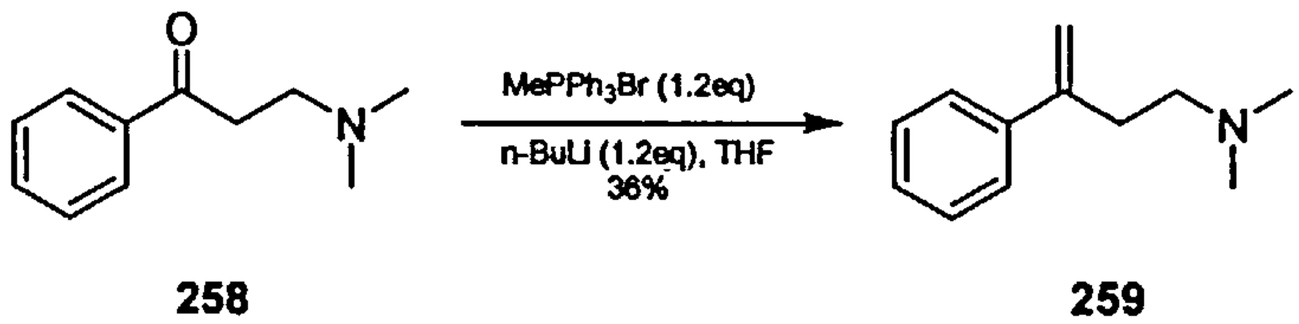
Scheme 59

With aminoalkyl styrenes **257** and **254** at hand, it was now possible to try the photochemical cyclisation. Preliminary attempts using a low-pressure mercury lamp in a quartz vessel resulted in only starting material even after prolonged irradiation. At this stage, it seemed sensible to reproduce one of the results obtained by Aoyama[126], to try and acquire a greater understanding of the irradiation process and conditions employed. It was decided to repeat the reaction depicted in scheme 60, since the

photochemical precursor could be prepared easily in one step from Wittig reaction on its corresponding Mannich base.

Synthesis of 4-(dimethylamino)-2-phenyl-1-butene (259).

Wittig reaction on commercially available β-dimethylamino propiophenone **258** gave the desired styryl amine **259** in moderate yield with all data identical to that reported (Scheme 60).[126]

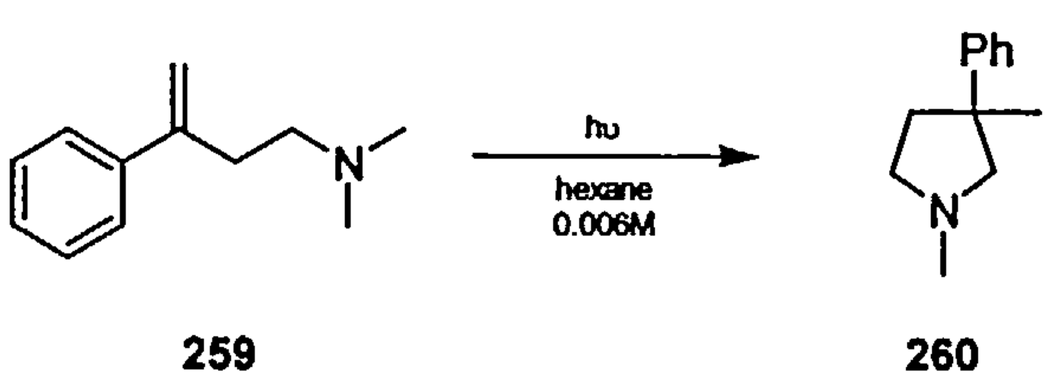


258 **259**

Scheme 60

Synthesis of 1,3-dimethyl-3-phenylpyrrolidine (260).

Styryl amine **259** was then subjected to irradiation using a medium pressure lamp, carried out in a quartz tube as a 0.006M solution in hexane. By proton-NMR the crude reaction mixture was 95% complete and displayed identical signals to that reported.[126]

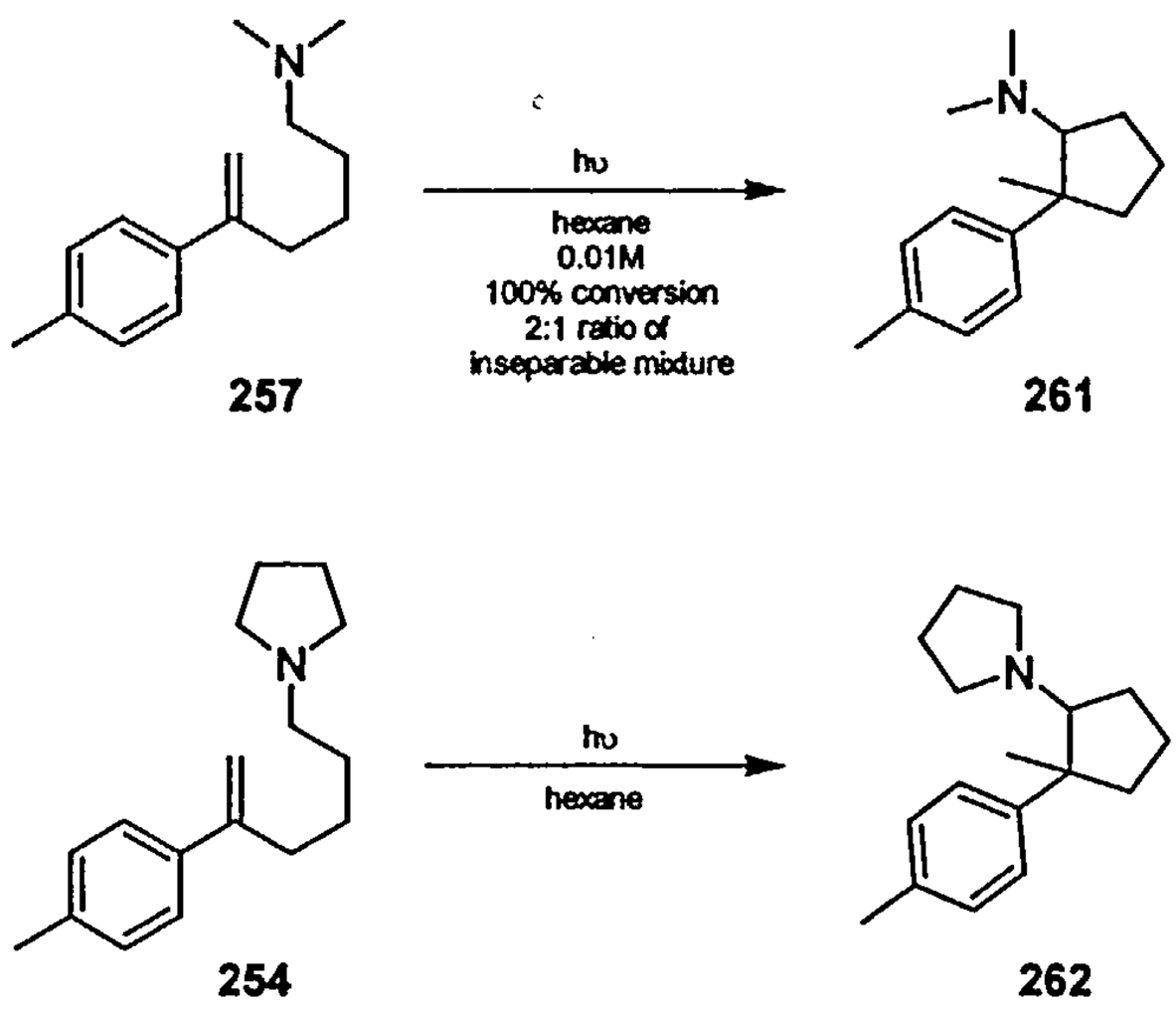


259 **260**

Scheme 61

Synthesis of dimethyl-(2-methyl-2-p-tolyl-cyclopentyl)-amine (261) and 1-(2-Methyl-2-p-tolyl-cyclopentyl)-pyrrolidine (262).

Photochemical cyclisation under similar conditions on aminoalkyl styrenes **257** and **254** led to cyclised adducts **261** and **262**. Irradiation of aminoalkyl styrene **257** gave an inseparable mixture of diastereomers as a 2:1 ratio by NMR and showed >95% conversion with all the characteristic signals in place. The products were not isolated and further efforts were focused towards the synthesis of styryl amine **239**, containing the geminal dimethyl groups.

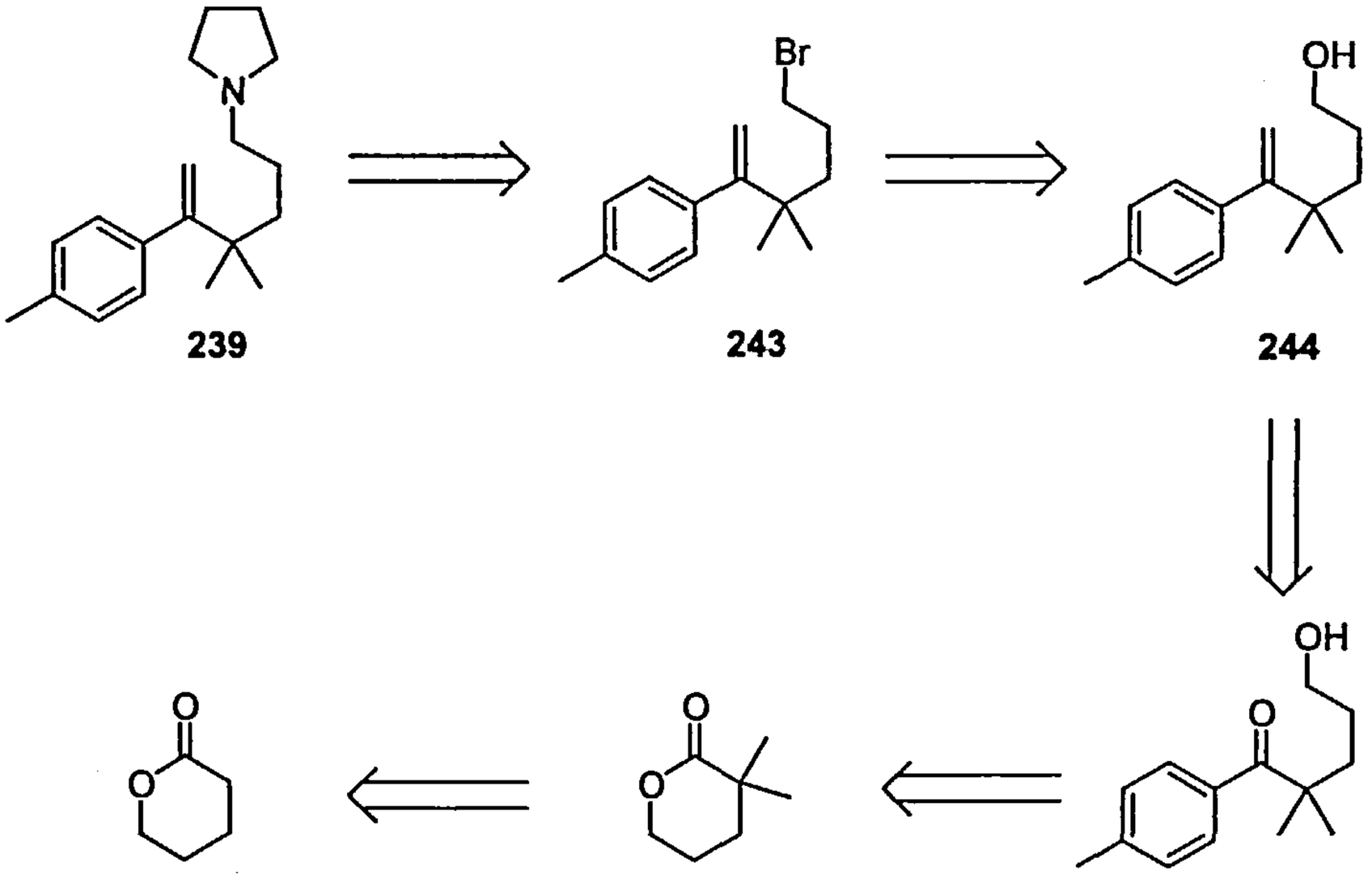


Scheme 62

2.2.2 Retrosynthetic analysis II.

At this stage that a more direct route to compound **239** was envisaged via ring opening of a lactone already containing the geminal dimethyl groups in the α-position **264**. This would avoid the somewhat circuitous route outlined in scheme 51 which involves protection of the alcohol as an acetal before introducing the geminal dimethyl moiety.

A search in the literature showed that α, α-dimethyl-δ-valerolactone **264** is known[127] and can be made from sequential alkylation of the parent δ-valerolactone **249**.[128] Ring opening of the lactone **264** should yield compound **263** which could undergo a Wittig reaction to form the alkene **244**. Converting the alcohol functionality to the bromide followed by coupling with the amine should furnish the photochemical precursor **239**.



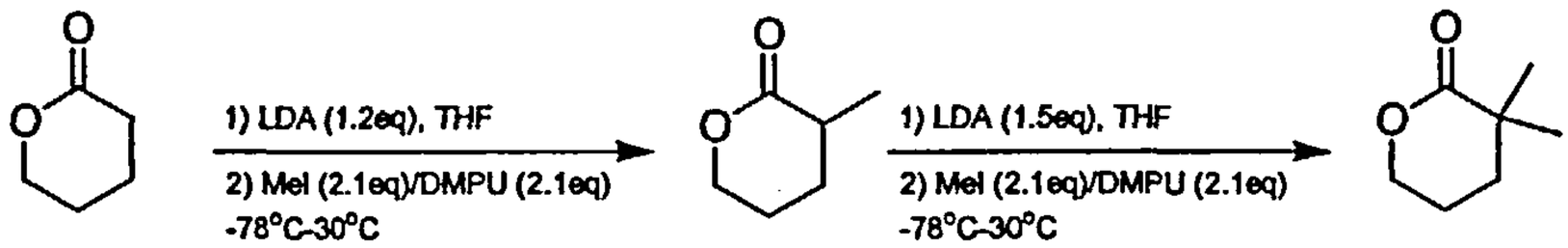
239 **243** **244**

249 **264** **263**

Scheme 63

Synthesis of α,α-dimethyl-δ-valerolactone (264).

This compound had been previously obtained by Schlessinger.[128] It was found that carrying out the reaction in two stages as depicted in scheme 64 resulted in better yields and cleaner reactions. Deprotonation of the α-proton using LDA forms the enolate, which is quenched at -30°C by the electrophile iodomethane. The precedented procedure utilised THF as solvent, however under these conditions the reaction was found to give mainly starting material. Adding the aprotic solvent DMPU (3 equivalents) afforded better results, giving the mono-alkylated product **265**, which was used in the next step without further purification. Repeating the reaction on the mono-alkylated product furnished the dialkylated lactone **264**, which was sufficiently pure to be carried forward to the next step without further purification (Scheme 64).

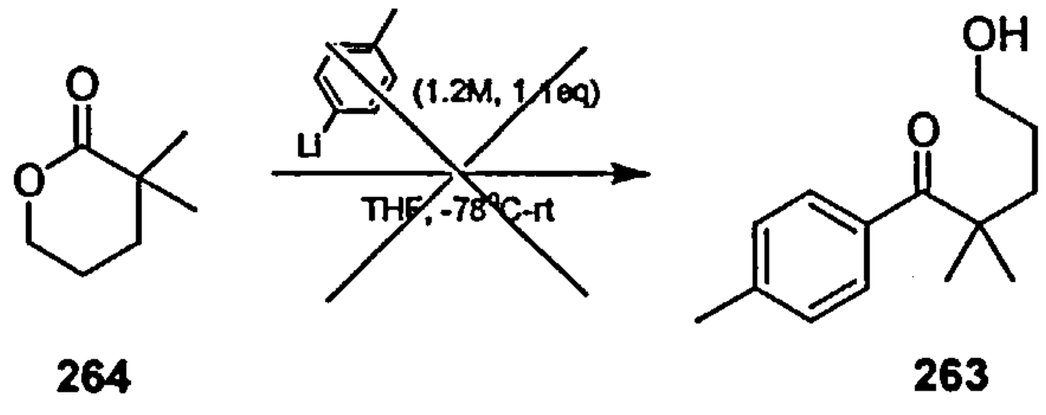


249 265 264

Scheme 64

Ring opening of α,α-dimethyl-δ-valerolactone (264).

Attempts to ring open the lactone under similar conditions to that employed in scheme 52 met with failure, resulting in complicated mixtures of products. This observation was in accordance with the literature, which also reported the ring-opening of the same lactone to be unsuccessful (Scheme 65).[119]



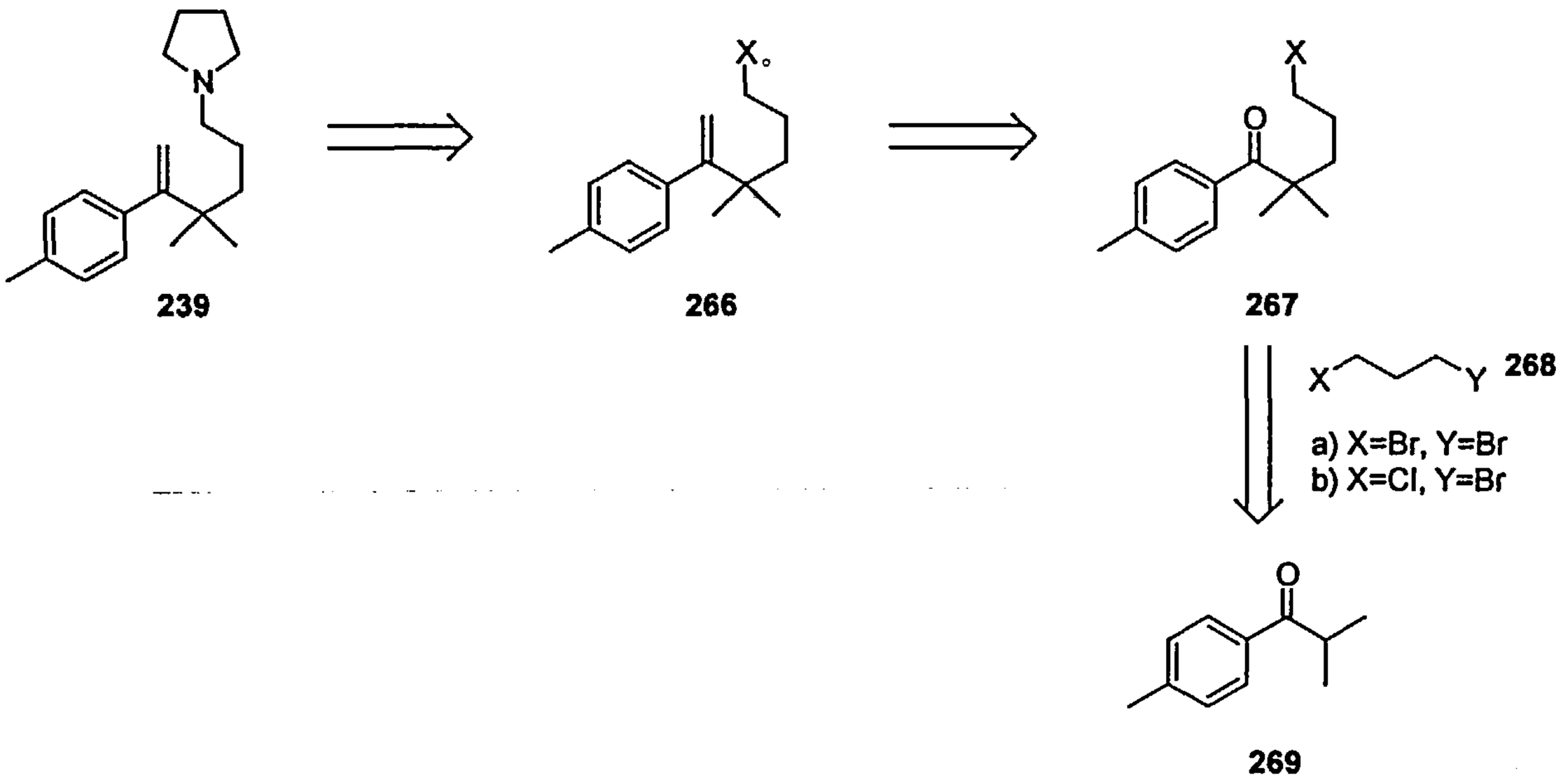
264 **263**

Scheme 65

In view of these results, a new approach to the photochemical precursor **239** with both geminal dimethyl groups in place was sought.

2.2.3 Retrosynthetic analysis III

Another possible route to compound **239** could be visualised from 4-methyl isobutyrophenone **269**. Generation of the enolate by deprotonation of **269** at the α-carbon followed by alkylation using the 1,3-dibromo propane **268a** or 1-bromo-3-chloropropane **268b** should give the halo-ketone **267**. To complete the synthesis, all that would be required would be a Wittig reaction on **267** followed by conversion of the resulting alkyl halide **266** to the required amine **239**. Compound **269** could be prepared from a Friedel-Crafts acylation of toluene (Scheme 66).



239 266 267 269

Scheme 66

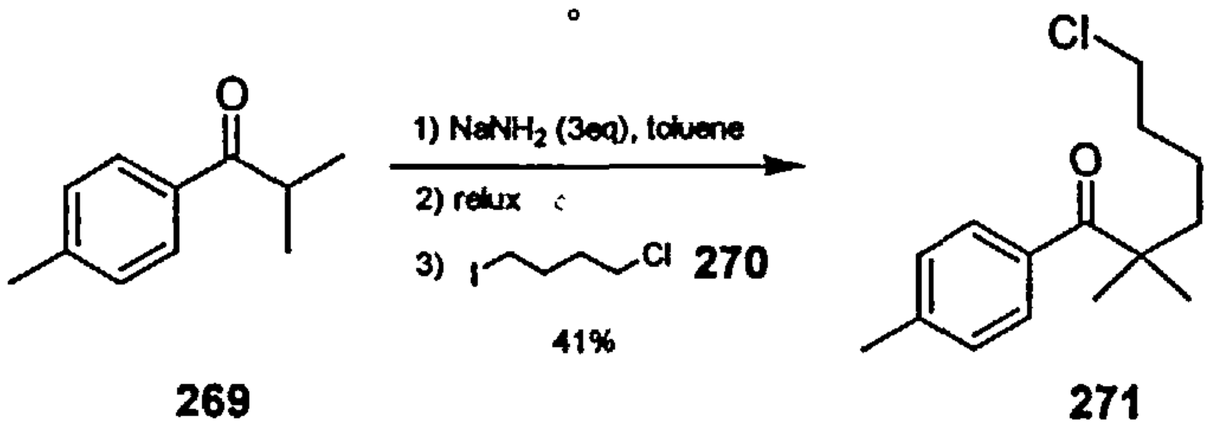
Synthesis of 4-methyl isobutyrophenone (269).

Compound **269** was prepared in a straightforward manner by adaptation of a literature procedure.[129] Friedel Crafts acylation in the presence of toluene at 60°C (3h) afforded **269** in an excellent 98% yield with all data identical to that reported.[130]

Since the 1-carbon homologated dihaloalkane, 1-chloro-4-iodobutane was readily available in the laboratory, initial attempts were carried out utilising this.

Synthesis of 6-Chloro-2,2-dimethyl-1-p-tolyl-hexan-1-one (271).

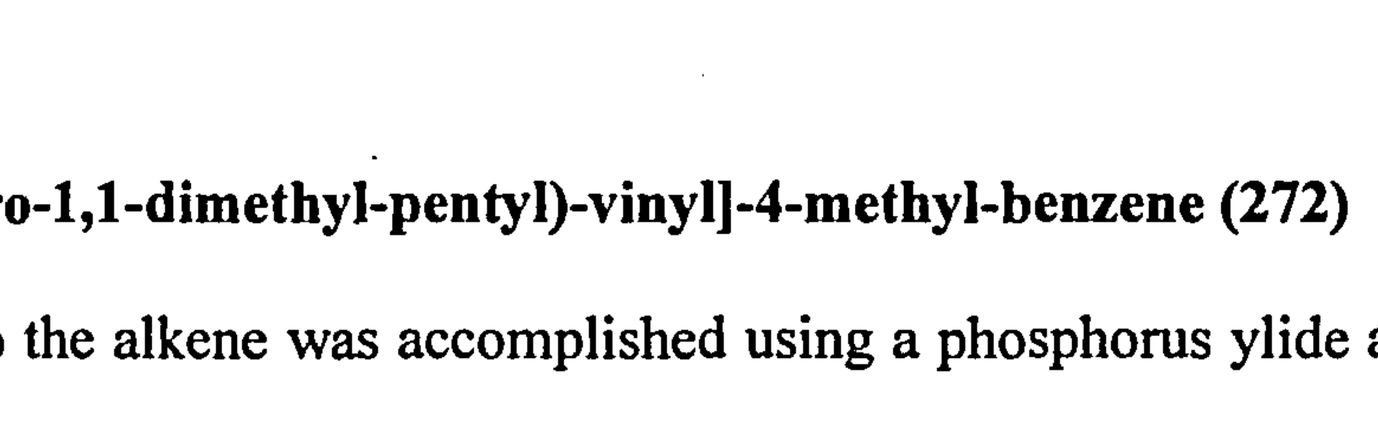
Generation of the enolate of **269** using sodium amide[131] followed by regioselective S_N2 substitution of 1-chloro-4-iodobutane **270** gave compound **271** in moderate yield. The product was fully characterised by spectroscopic data and displayed all the expected peaks (IR, ^1H NMR, ^{13}C NMR, high and low resolution mass spectra) (Scheme 67).



Scheme 67

1-[1-(5-Chloro-1,1-dimethyl-pentyl)-vinyl]-4-methyl-benzene (272)

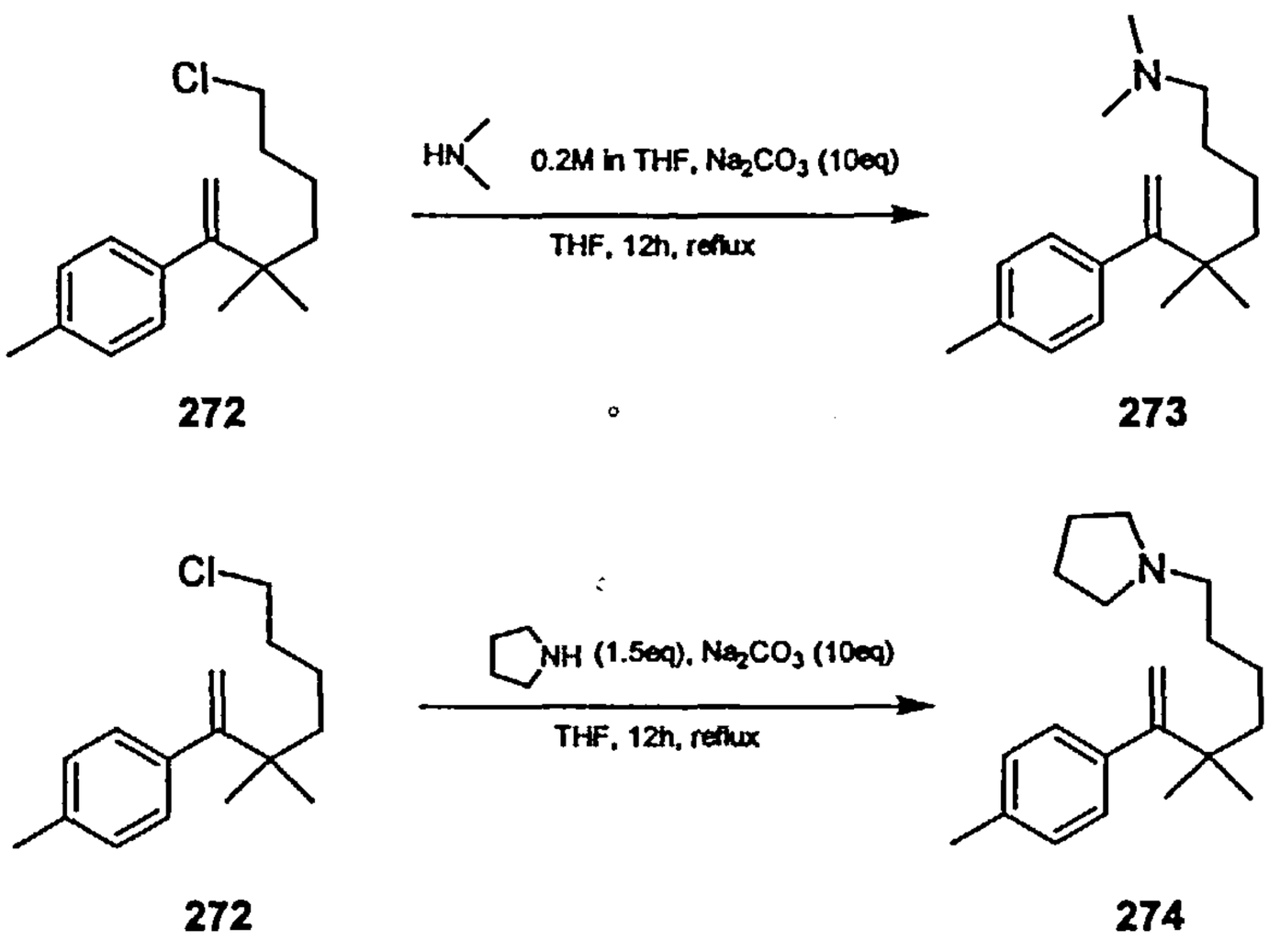
Conversion to the alkene was accomplished using a phosphorus ylide and proceeded in the usual manner. The product was purified by flash column chromatography and was obtained in moderate yield (42%), sufficient for our purposes. All spectroscopic data correlated well with expectations (IR, ^1H NMR, ^{13}C NMR, mass spectra) (Scheme 68).



Scheme 68

Synthesis of aminopentyl styrenes (273) and (274).

Finally, **272** was subjected to the usual substitution procedure with dimethylamine or pyrrolidine in the presence of sodium carbonate to afford the amines **273** or **274.** The products did not require any further purification and the crude ^{1}H NMR showed all the characteristic signals.



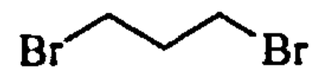
272 **273**

272 **274**

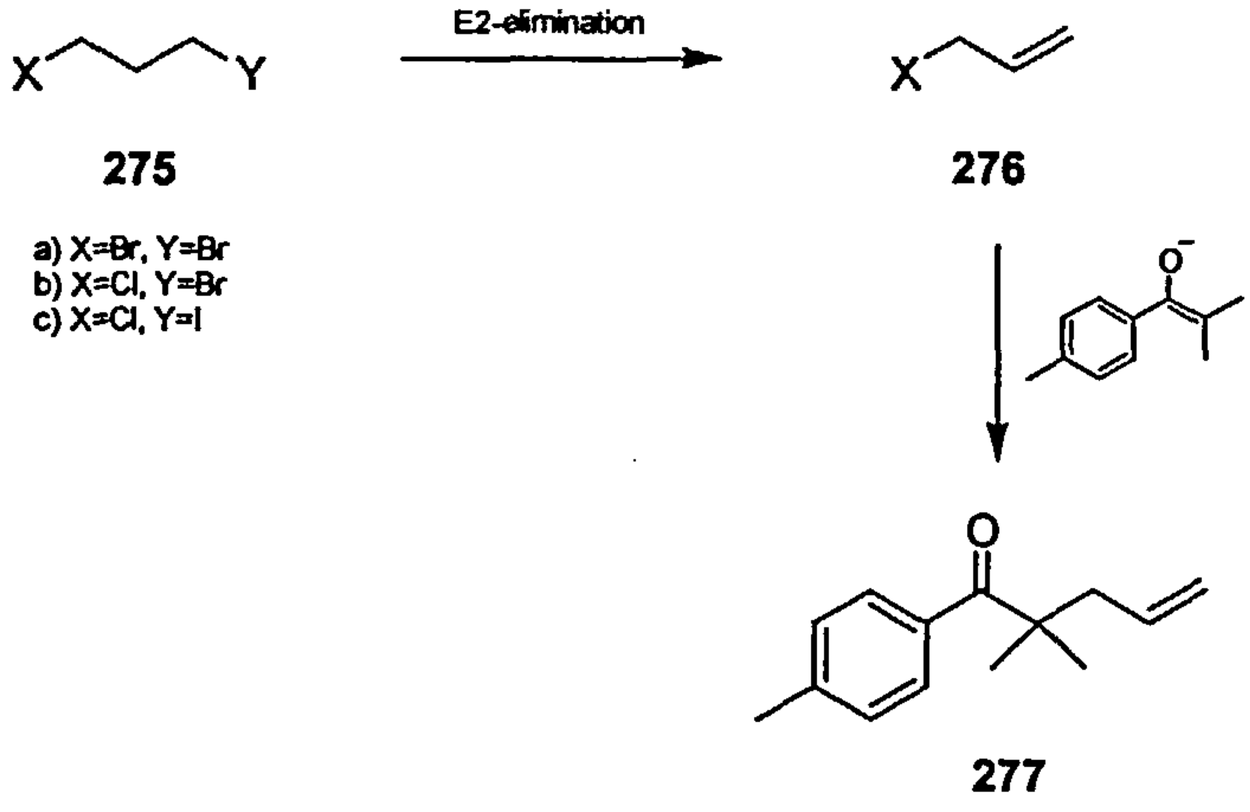
Scheme 69

It was anticipated that repetition of the sequence above using the correct dihalo-alkane i.e. dihalo-propane, should furnish the requisite precursor. Unfortunately, all attempts to repeat the sequence resulted in failure. The results of attempted alkylation of **269** using 1,3-dibromopropane **275a**, 1-bromo-3-chloropropane **275b** and 1-chloro-3-iodopropane **275c** under a variety of conditions are listed in table 2 below.

Table 2: different reaction conditions for alkylation of **269**.

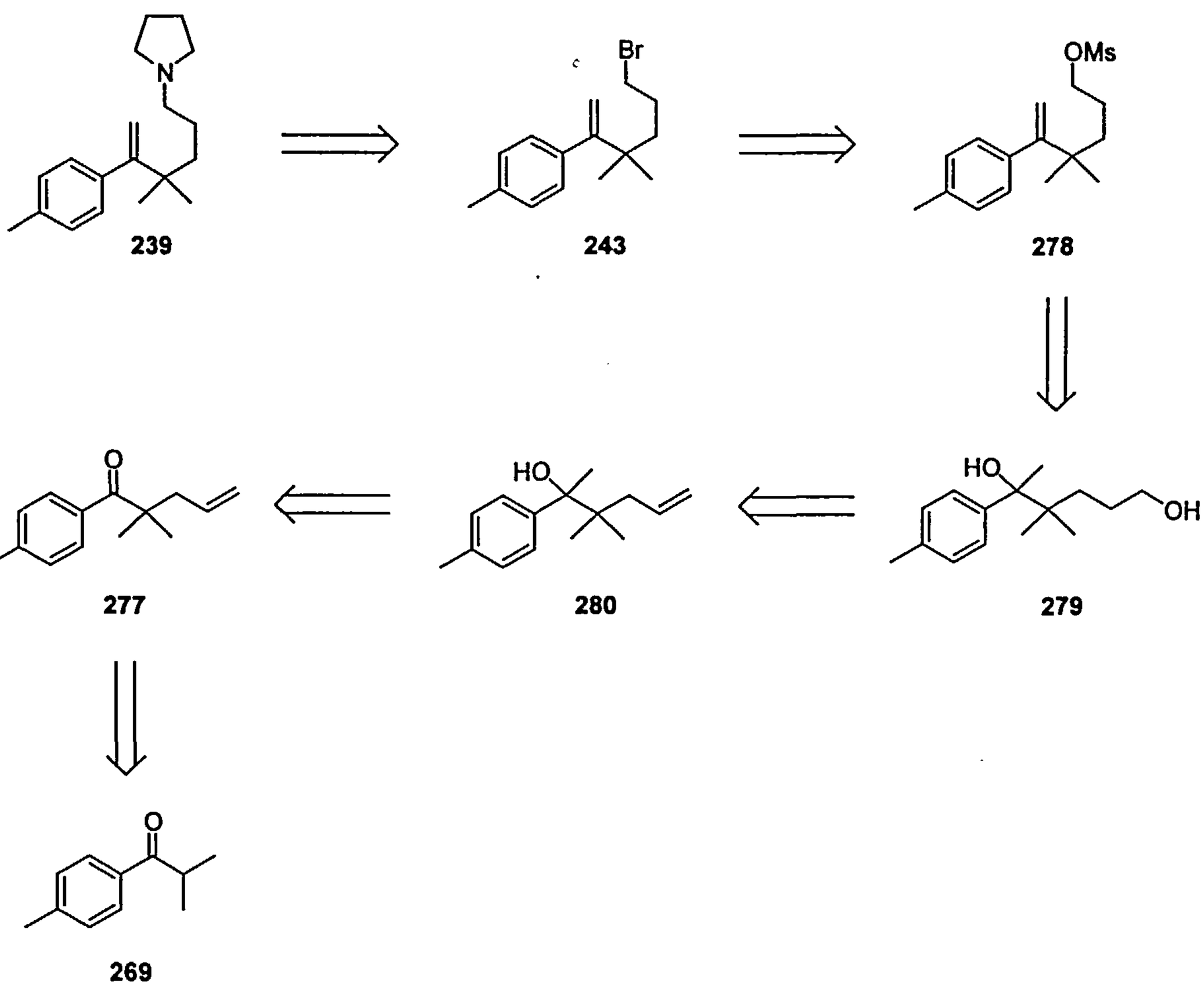
Reaction conditions	Result
$NaNH_2$ (1eq), toluene reflux.  (2eq)	**269** and **277**
$NaNH_2$ (2eq), toluene reflux.  (1.5eq)	**269** and **277**
$NaNH_2$ (3.2eq), toluene reflux.  (2.2eq)	**269** and **277**
$NaNH_2$ (1eq), toluene reflux.  (2eq)	**269** and **277**
$NaNH_2$ (1.5eq), toluene reflux.  (2eq)	**269** and **277**
$NaNH_2$ (2eq), toluene reflux.  (1.5eq)	**269** and **277**
$NaNH_2$ (3eq), toluene reflux.  (1.5eq)	**269** and **277**
$NaNH_2$ (3eq), toluene reflux.  (2.5eq)	**269** and **277**

In all instances, the alkylation resulted in mainly elimination product **277** accompanied by small amounts of starting material, inconsistent with previous success. The elimination product is probably a consequence of E2-elimination on the dihalo-propane to form the allylhalide, which is subsequently quenched by the enolate. Reducing the number of equivalents of the base in an attempt to retard the elimination was unsuccessful, since the enolate of the starting material could also potentially act as a base (Scheme 70). It became apparent that the eliminated product could still be utilised since hydroboration and subsequent oxidation of the double bond would place the alcohol on the least hindered terminal position, which could then be converted to the bromide via the procedure already depicted in scheme 58.



Scheme 70

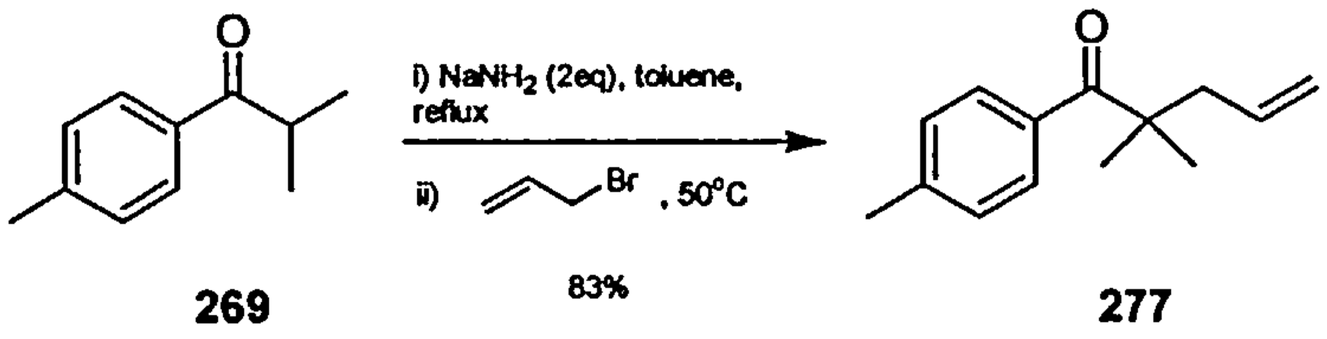
A search of the literature produced a procedure by Srikrishna[132] who utilised compound **278** as an intermediate to the synthesis of desired alkylbromide **243.** The main features of this synthesis involves alkylation of 4-methylisobutyrophenone **269** with allylbromide to give the keto-alkene **277.** Grignard reaction utilising methylmagnesium iodide furnishes the alcohol **280.** Hydroboration followed by oxidation of the alkene moiety produces the diol **279,** which is subjected to mesylation conditions. This causes dehydration of the tertiary alcohol and mesylation of the primary alcohol. The resulting enemesylate **278** can then be converted to the bromide using the procedure described in scheme 58.



Scheme 71

Synthesis of 2,2-Dimethyl-1-p-tolyl-pent-4-en-1-one (277).

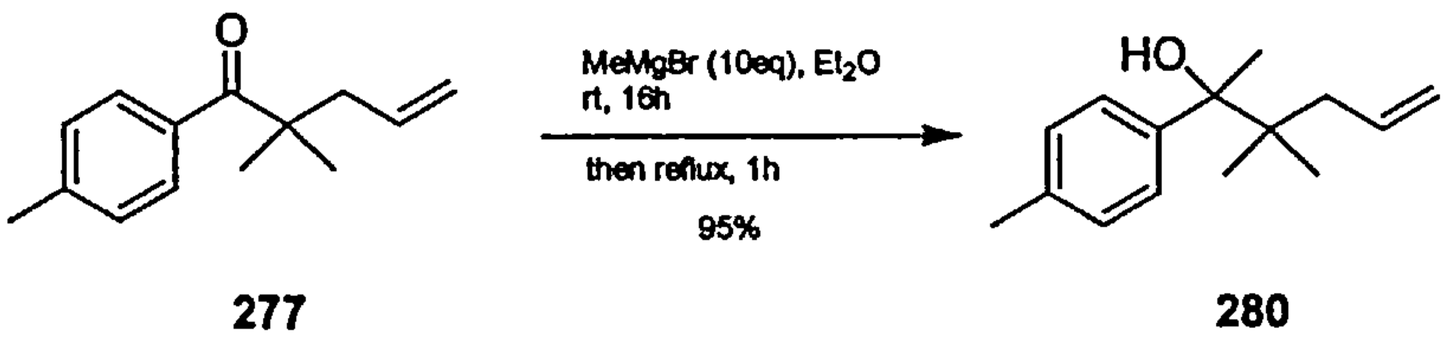
Commencing from compound **269**, generation of the enolate of **269** using $NaNH_2$ in refluxing toluene followed by quenching with allyl bromide at 50°C furnished the allylated ketone **277** with both geminal dimethyl groups in place in 83% yield.



Scheme 72

Synthesis of 3,3-Dimethyl-2-p-tolyl-hex-5-en-2-ol (280).

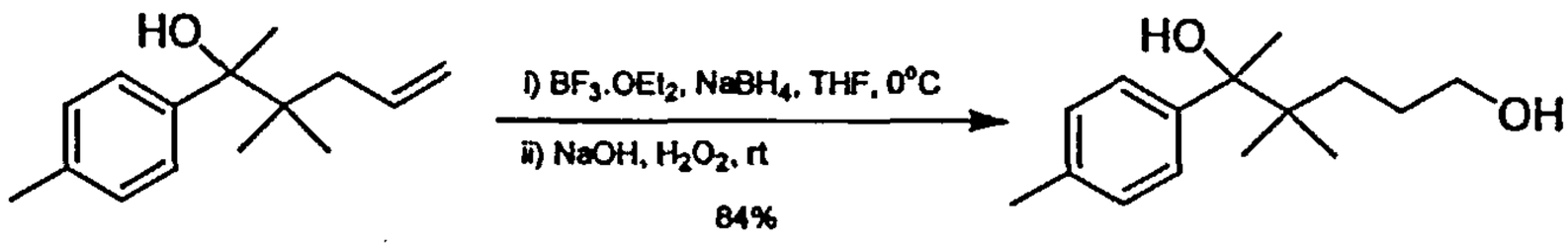
The synthesis of **280** proceeded without incident. Addition of methylmagnesium iodide in refluxing ether to compound **277** produced the tertiary alcohol in excellent 95% yield, exceeding that reported in the literature.[132] The product was fully characterised and gave spectroscopic data identical to that reported (IR, ^1H NMR, ^{13}C NMR and low-resolution mass spectra).



Scheme 73

Synthesis of 4,4-Dimethyl-5-p-tolyl-hexane-1,5-diol (279).

Hydroboration followed by oxidation furnished the diol **279** in 84% yield, identical to that reported in the literature.[132] The alkylborane is formed via hydroboration at the least hindered terminal end of the alkene. This intermediate was not isolated and converted to the alcohol using alkaline hydrogen peroxide (Scheme 74).

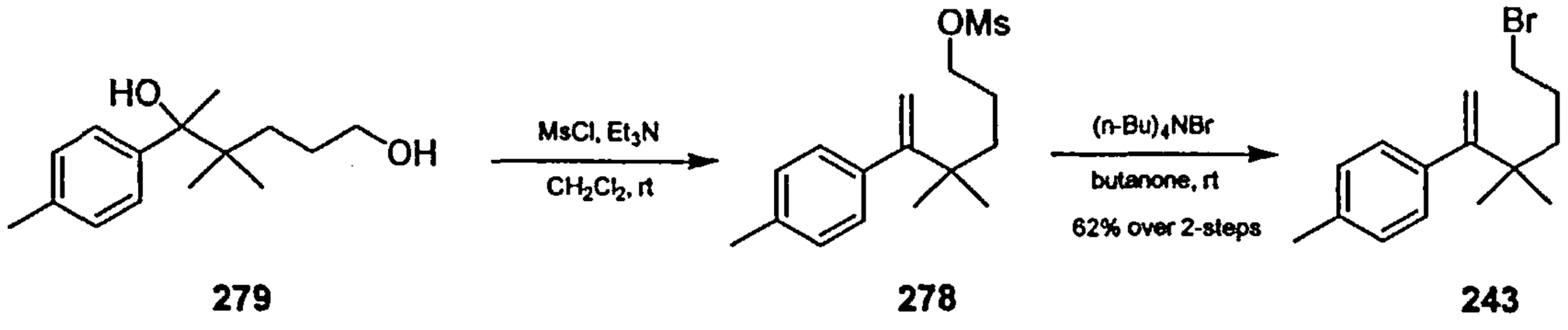


280 **279**

Scheme 74

Synthesis of 3,3-dimethyl-6-bromo-2-(4-methylphenyl)-1-hexene (243).

Addition of diol **279** to the sulfene, derived from methanesulfonyl chloride and triethylamine resulted in simultaneous mesylation of the primary alcohol and dehydration of the tertiary alcohol. The resulting enemesylate **278** was not rigorously purified but converted directly to the bromide via nucleophilic displacement in the presence of TBAB and butan-2-one. The product alkylbromide **243** was isolated by flash column chromatography in 62% yield over the two steps and gave spectroscopic data identical to that reported in the literature (IR, ^{1}H NMR, ^{13}C NMR and low-resolution mass spectra) (Scheme 75).[132]

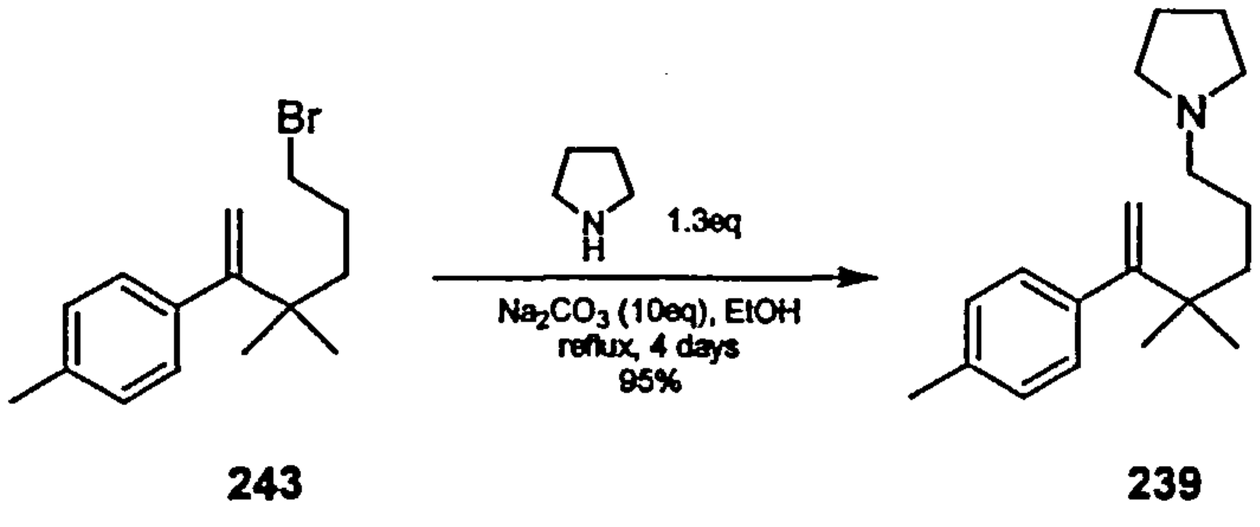


279 278 243

Scheme 75

Synthesis of 1-(4,4-Dimethyl-5-p-tolyl-hex-5-enyl)-pyrrolidine (239).

The key intermediate **239** required to test the cyclisation was readily prepared in multigram quantities. Coupling of pyrrolidine with alkylbromide **243** following a similar procedure to that described earlier proceeded smoothly.[125] The product aminoalkyl styrene **239**, obtained in 95% yield was purified by flash column chromatography and was fully characterised by spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, low and high-resolution mass spectra) (Scheme 76).



243 239

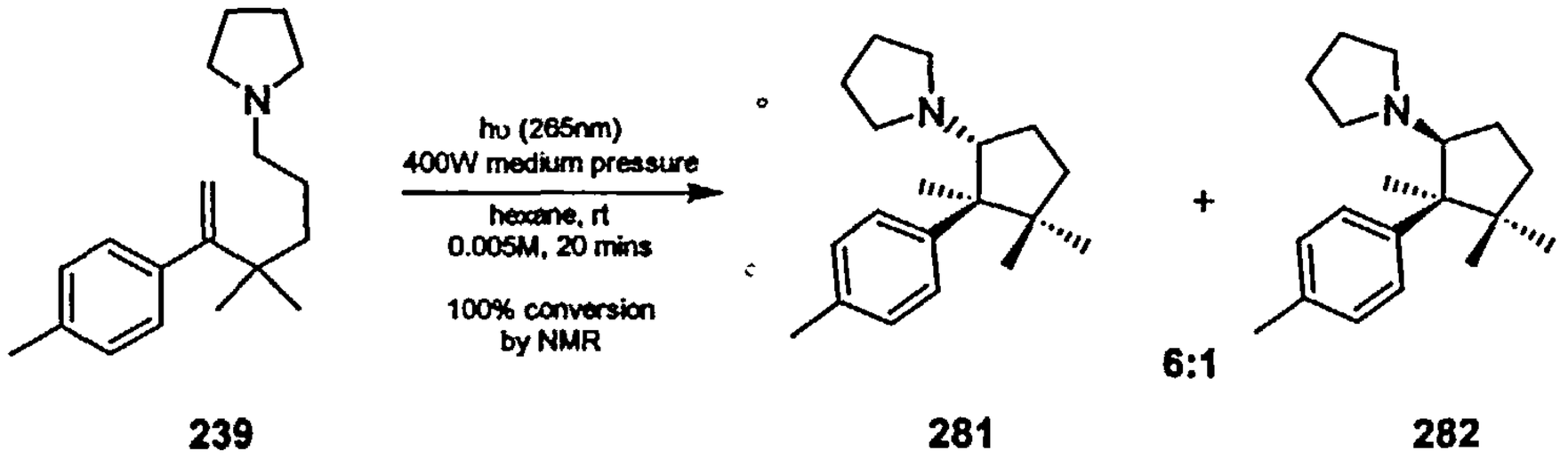
Scheme 76

Having achieved a synthesis of the photochemical precursor **239**, construction of the cyclopentane ring via a photomediated cyclisation, under similar conditions to that reported in scheme 59, was attempted.

2.3 Synthesis of (±)-cuparene 1

Synthesis of *trans*-1-(2,3,3-Trimethyl-2-p-tolyl-cyclopentyl)-pyrrolidine (281) and *cis*-1-(2,3,3-Trimethyl-2-p-tolyl-cyclopentyl)-pyrrolidine (282).

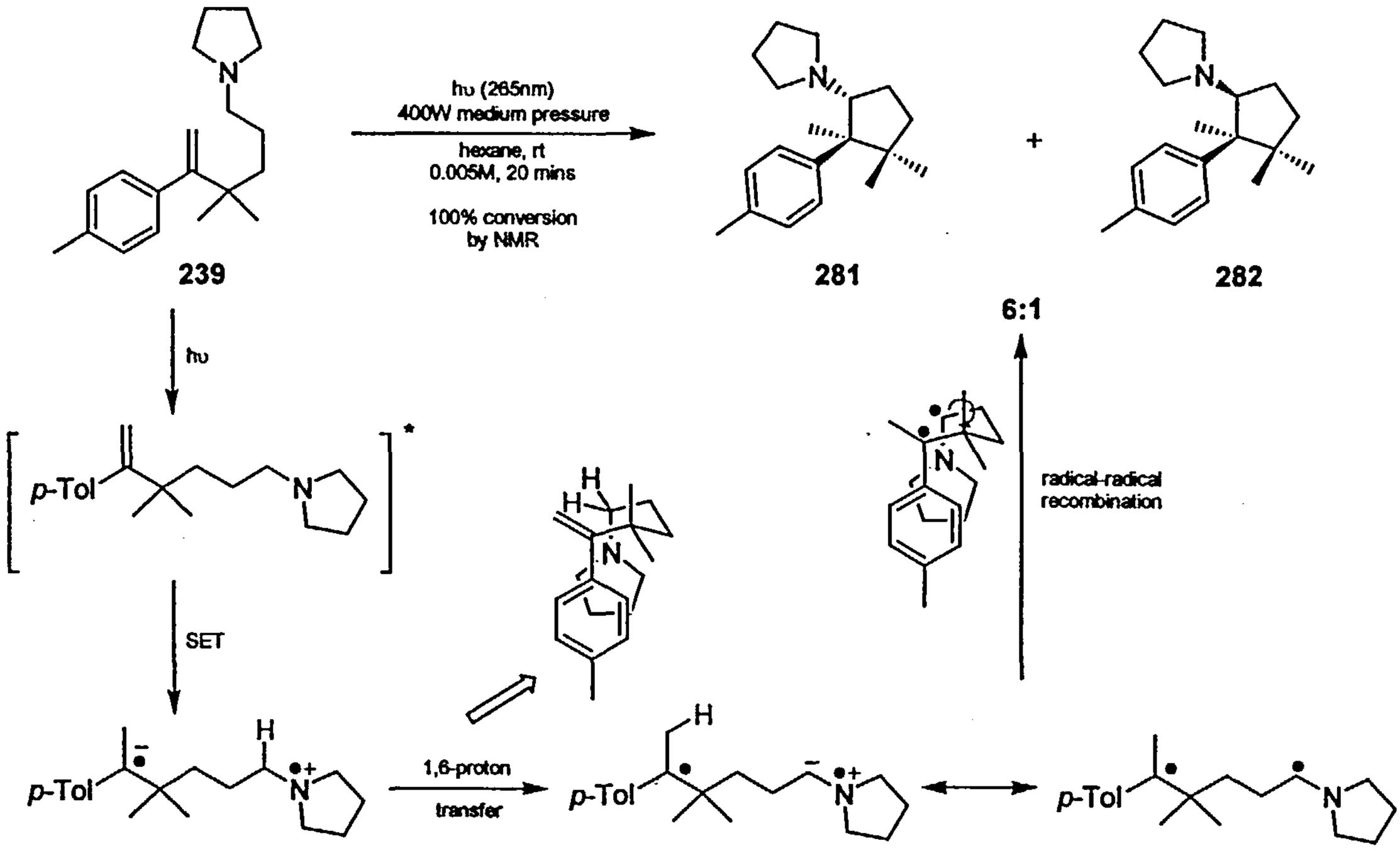
Irradiation of aminobutyl styrene **239** in a hexane solution, carried out in a quartz vessel under a medium pressure mercury lamp, resulted in efficient formation of cyclised adducts **281** and **282** as a separable 6:1 ratio of diastereoisomers. Prolonged irradiation results in decomposition to several unidentifiable products (Scheme 77).



239 **281** **282**

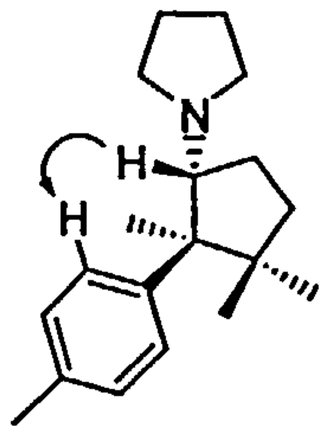
Scheme 77

Product formation for both diastereoisomers can reasonably be explained via the intermediacy of a 1,5-biradical generated from 1,6-proton transfer from N-methyl to the styrene β-carbon. In non-polar solvents, the styryl-amine exciplex adopts a folded conformation, which maximises orbital overlap and allows for H-transfer to occur via a least motion pathway.[108, 115] This places the amine and arene adjacent to one another as indicated in scheme 78. Suggesting that the radical-radical recombination step has a lifetime associated with it since rotation around the styrene-carbon bond must occur in order to lead to the observed selectivity of 6:1 in favour of the *trans* substituted cyclopentane adduct **281**. This shows that the dimethyl group in the connecting chain can be tolerated (Scheme 78).

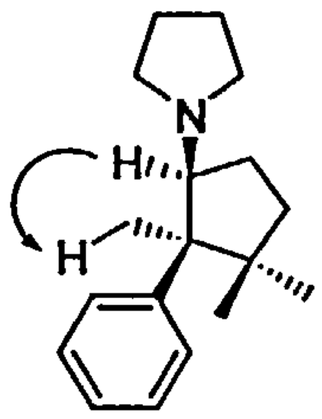


Scheme 78

The combined yield of the two cycloadducts was 100% by NMR analysis of the crude reaction mixture, and the major diasteromer **281** was isolated in 62% yield by careful column chromatography. Adduct stereochemistry was assigned on the basis of ^{1}H-NMR data. The NOESY spectrum of the major isomer **281** displayed a cross peak between the methine proton α to nitrogen and the aromatic ring protons. No correlation between the adjacent methyl group on the cyclopentane ring was observed. In contrast the NOESY spectrum of the minor isomer **282** showed a strong cross peak correlating to the methine proton α to nitrogen and the adjacent methyl group on the cyclopentane ring but no correlation with the aromatic ring protons (Figure 7).



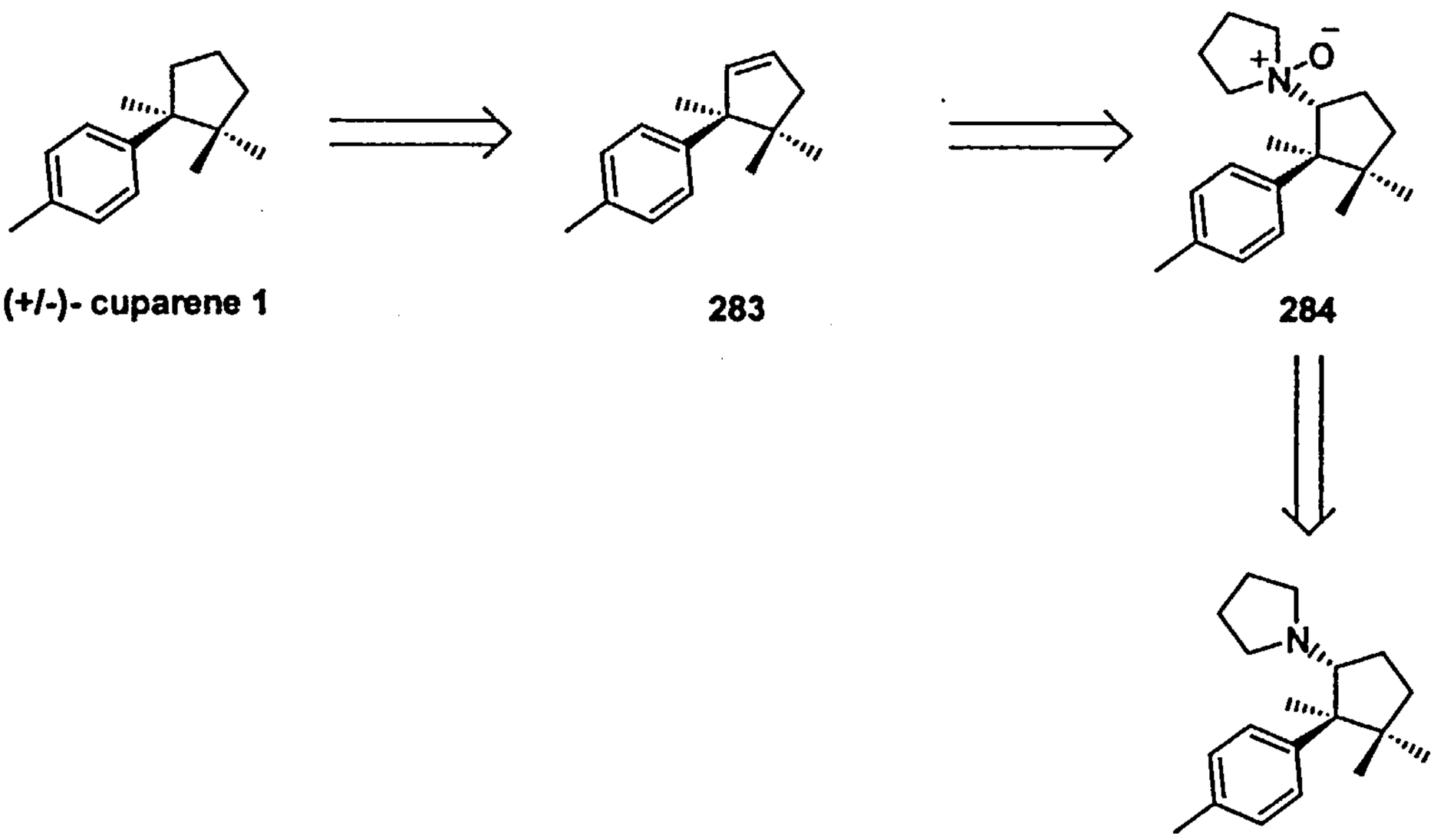
281



282

Figure 7

Conversion of the major cycloadduct **281** to cuparene required removal of the amine moiety. We envisaged that this could be achieved via Cope elimination[133] of the amine oxide[134] followed by hydrogenation of the resulting alkene, to furnish racemic cuparene **1** (Scheme 79).



(+/-)- cuparene 1

283

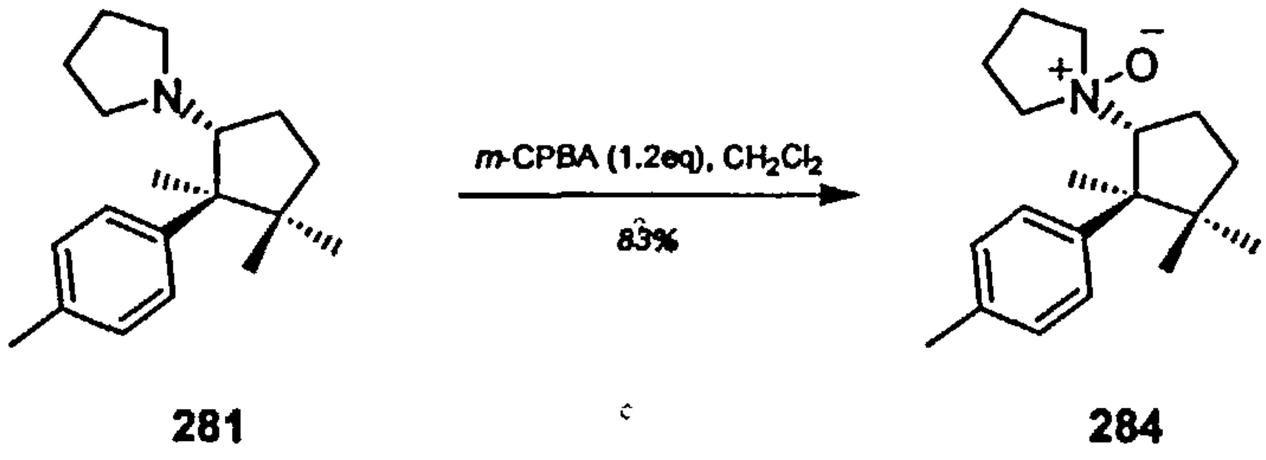
284

281

Scheme 79

Synthesis of 1-(2,3,3-Trimethyl-2-p-tolyl-cyclopentyl)-pyrrolidine-1-oxide (284).

Oxidation of the major cycloadduct **281** to the *N*-oxide **284** was readily achieved using *m*-CPBA in dichloromethane.[135] Excess oxidizing agent was quenched using $Na_2S_2O_3$ and the resulting pale brown sticky solid/oil was purified by flash column chromatography to afford a fluffy white solid in 83% yield. The product was fully characterised by ^1H, ^{13}C-NMR, IR spectroscopy, low and high-resolution mass spectrometry (Scheme 80).

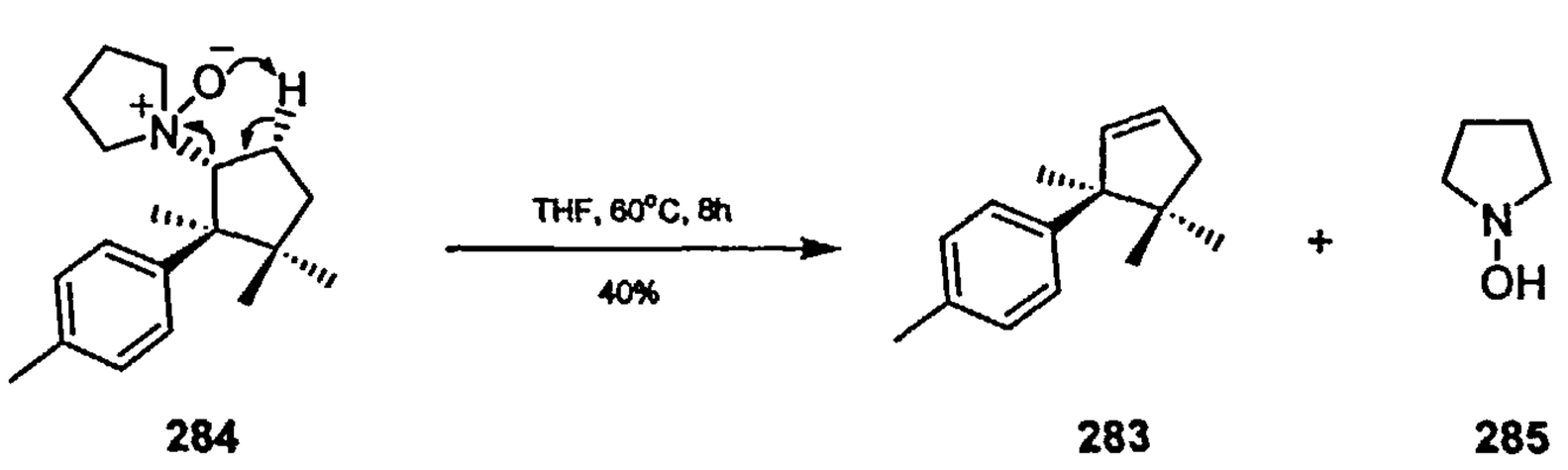


281 **284**

Scheme 80

Synthesis of 1-Methyl-4-(1,5,5-trimethyl-cyclopent-2-enyl)-benzene (283).

The thermally induced Cope elimination on **284** to produce alkene **283** proved to be more troublesome. Under a number of reaction condition, as indicated in the table below, the product was accompanied by significant amounts of other unidentifiable by-products leading to a yield at best of 40% in THF at 60°C over 8 hours (Scheme 81).



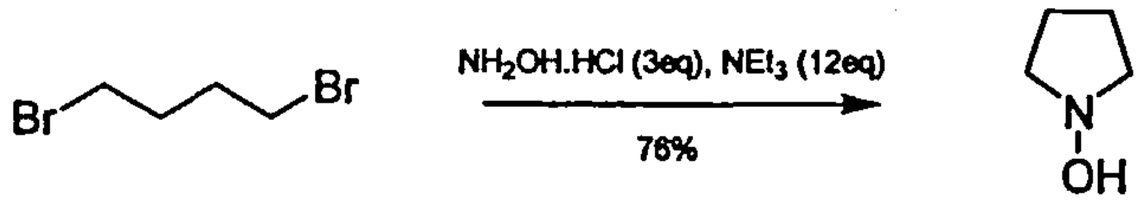
284 **283** **285**

Scheme 81

Mechanistically the *N*-oxide abstracts a β-hydrogen and cleaves the C_α-N bond to give alkene **283** and *N*-hydroxypyrrolidine **285**. This is an E_i *syn* elimination process, which proceeds via a five-membered planar transition state.[134] In the transition state both C_α-N and C_β-H bonds are extensively broken whilst C_α-C_β double bond character is developed.[133]

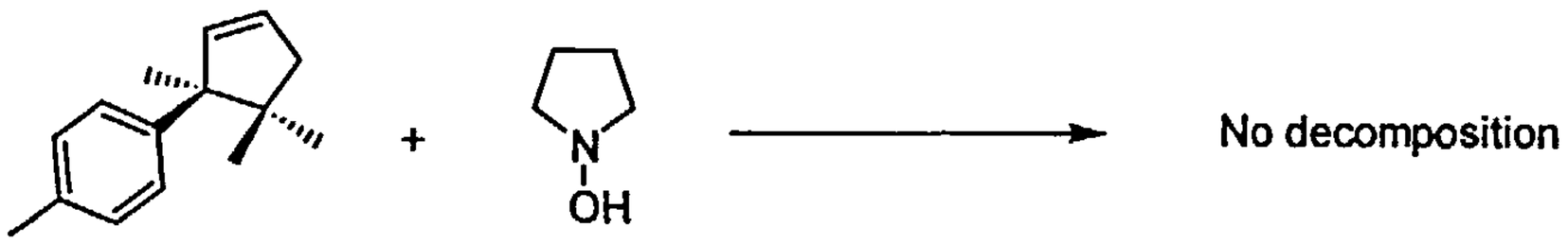
Ring cleavage of the *N*-oxide by abstraction of the β-hydrogen on the pyrrolidine ring as a means of a competing pathway seems to be unfavourable, since the elimination process would require all five atoms to be in the plane. Early studies by Cope suggest ring cleavage not to occur in six membered rings due to the difficulty of achieving a planar arrangement.[133]

Control experiments with independently synthesised *N*-hydroxypyrrolidine **285**,[136] prepared from commercially available 1,4-dibromobutane **286** and hydroxylamine hydrochloride, proved the alkene to be stable by ^{1}H-NMR under the reaction conditions and to temperatures exceeding 150°C in DMSO.



286 **285**

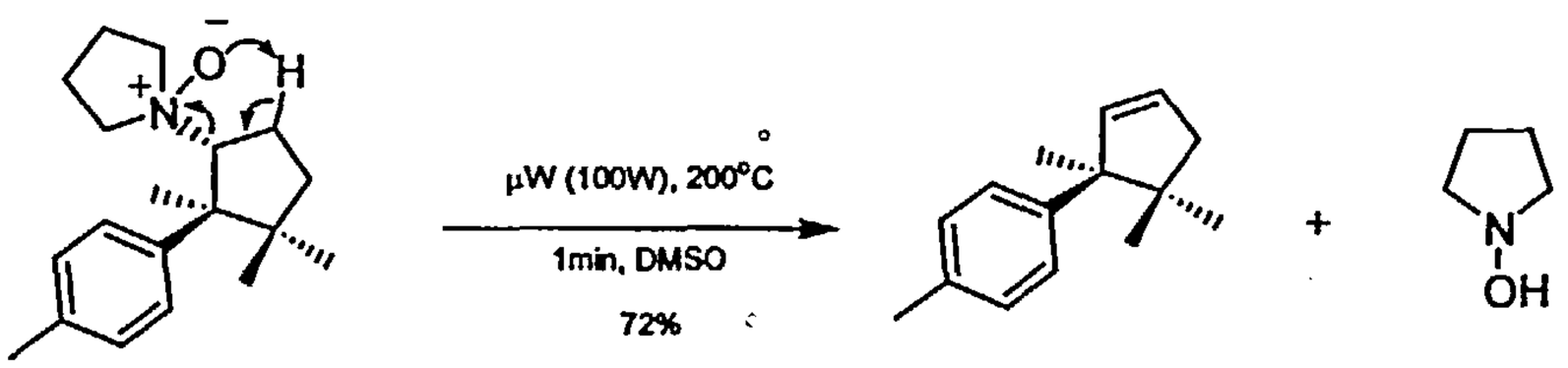
Scheme 82



283 **285**

Scheme 83

Eventually, it was discovered that yields could be greatly enhanced by performing the reaction in a microwave reactor. In practice a solution of the N-oxide **284** in DMSO was placed in a focussed microwave reactor chamber and the solution was warmed from 25°C to 200°C over a period of 1 minute at 100W. Standard workup and flash column chromatography gave alkene **283** in 72% yield as a colourless oil, which was fully characterised by standard spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, low and high-resolution mass spectra) (Scheme 84).



Scheme 84

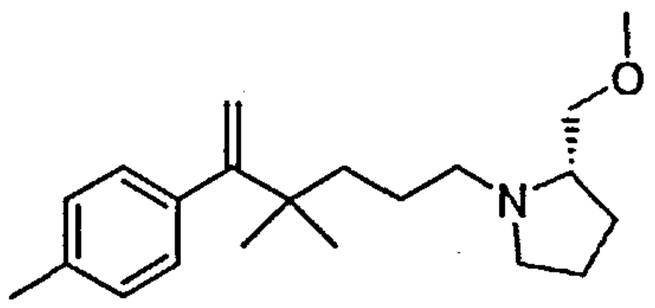
Synthesis of (±)-cuparene (1).

Hydrogenation of the double bond in **283** was accomplished without incident under atmospheric pressure to afford racemic cuparene **1**. The product was purified by flash column chromatography and gave spectroscopic data which was identical to that reported in the literature.[4, 5, 7]

Scheme 85

2.4 Syntheis of enantiomerically pure (*S*)-(–)-cuparene 22

It was envisaged that incorporating a chiral amine in place of pyrrolidine in the cyclisation precursor would render the above process asymmetric. Although a range of C_2-symmetric and non-C_2-symmetric chiral amines are known and have found widespread use in asymmetric synthesis, not all would act as suitable auxiliaries for this purpose. Of particular concern was the Cope elimination step, since this limits our choice to those amines that do not have a β-proton, which can achieve co-planarity in the transition state. The Cope elimination step should also allow for recovery of the auxiliary, albeit as a hydroxylamine which could be reduced back to the amine. For this reason attention was focussed towards the synthesis of both C_2-symmetric and non-C_2-symmetric cyclic variants displayed in figure **8** below.



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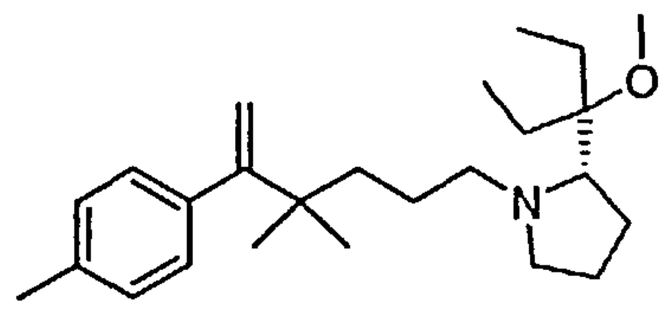

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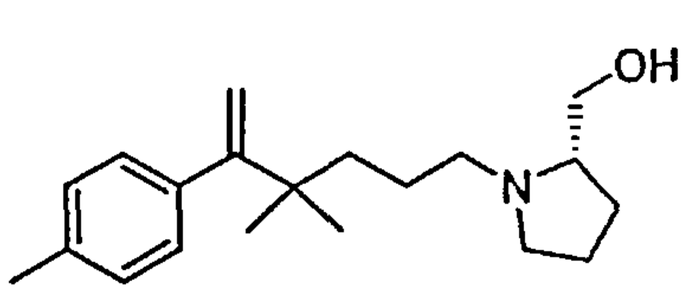

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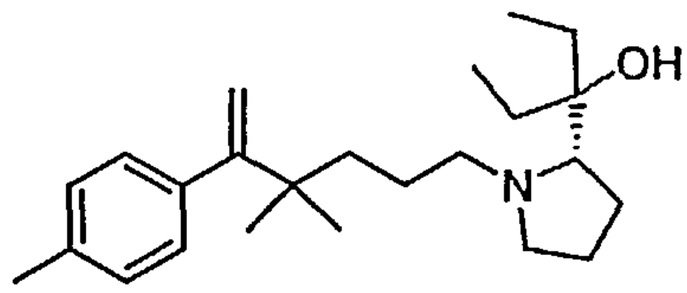

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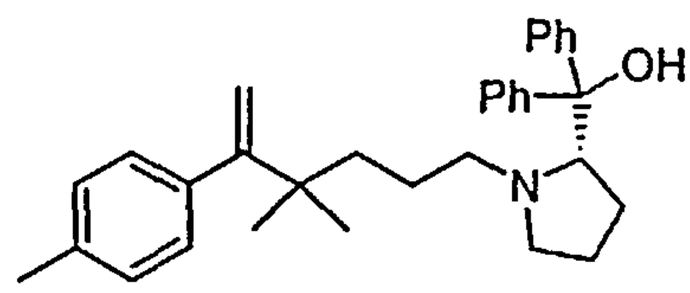

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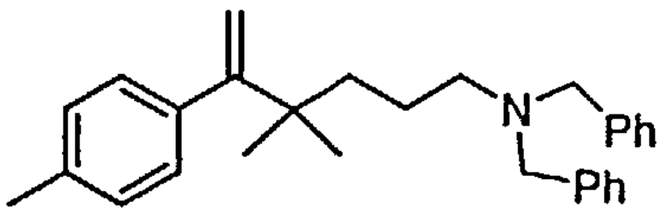

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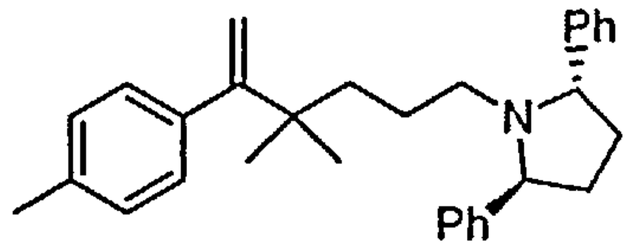

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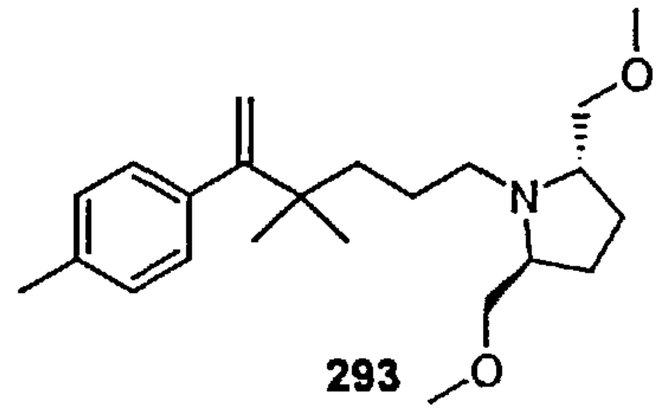
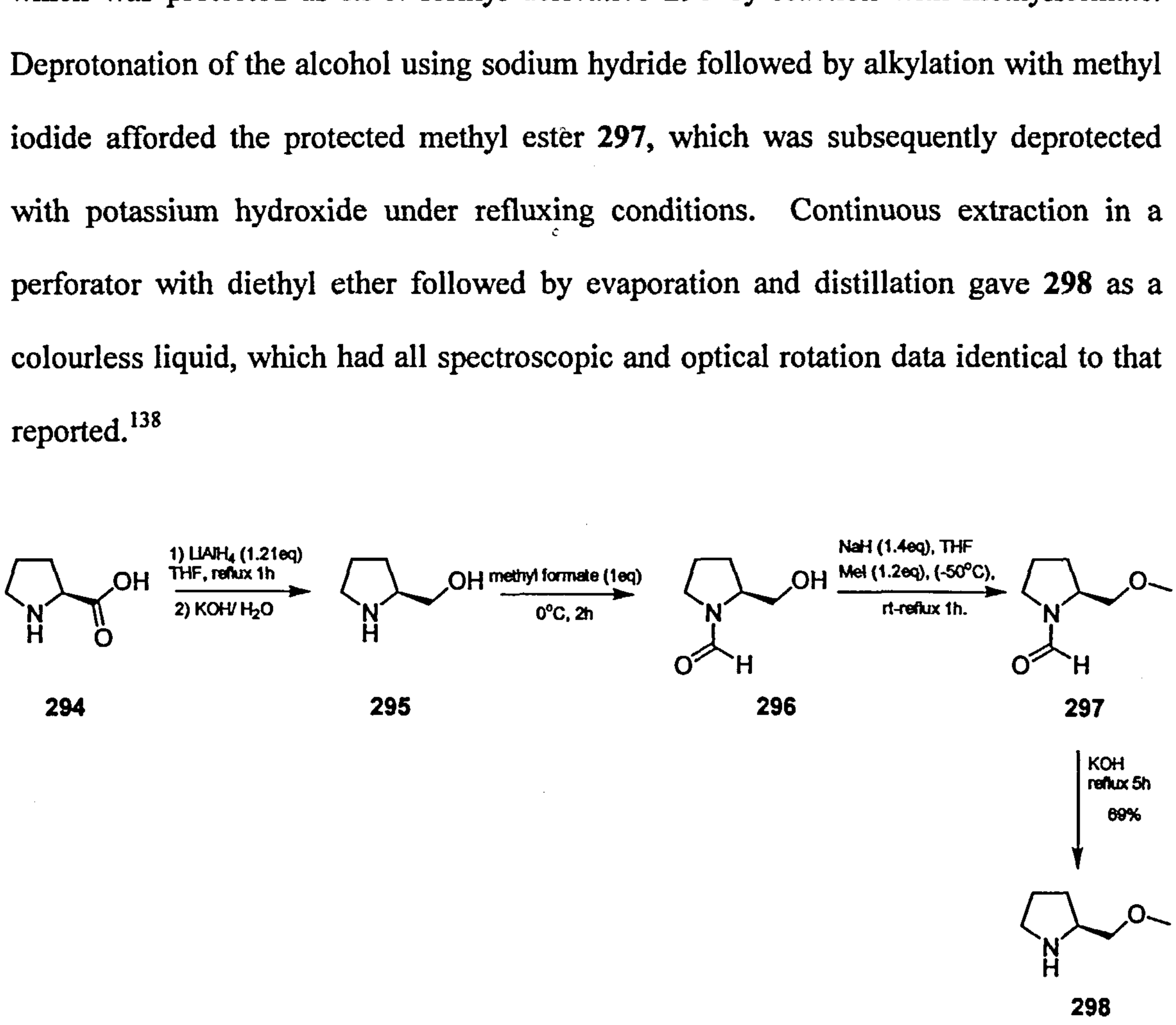


293

Figure 8

Synthesis of (*S*)-(+)-2-methoxymethylpyrrolidine (298).

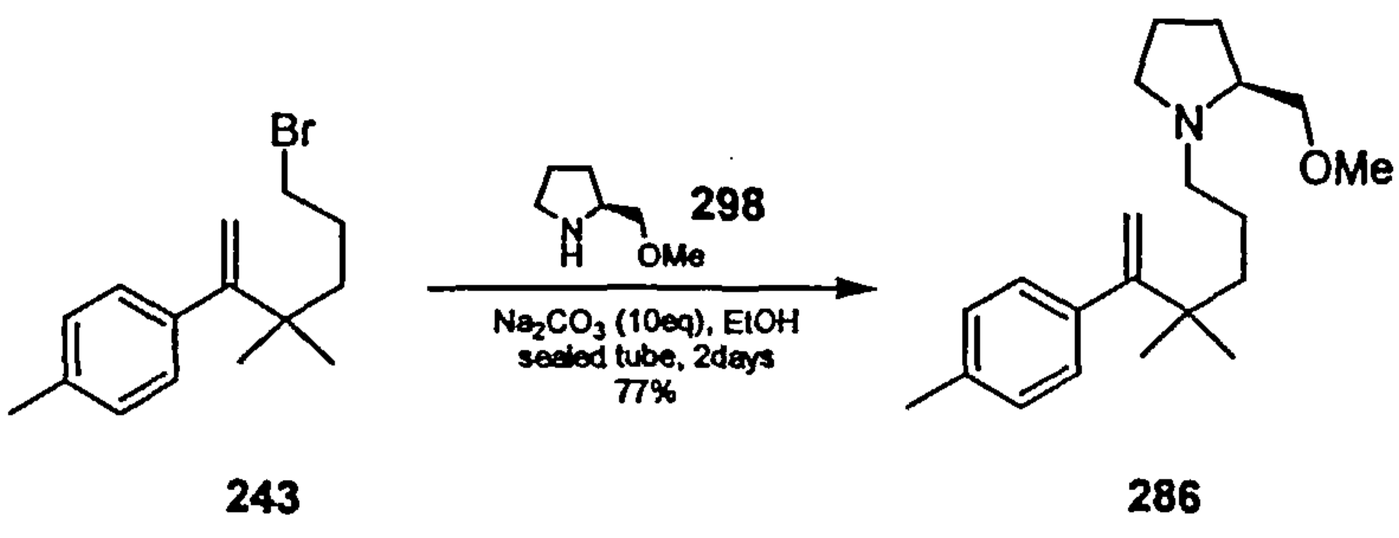
Early attempts began with the synthesis of the proline derived auxiliary SMP **298**. The synthetic utility of **298** as a chiral auxiliary in stoichiometric asymmetric synthesis has been demonstrated through a wide range of applications.[137] Following Enders protocol[138] SMP **298** was synthesised in multigram quantities from (*S*)-proline **294** via reduction of the acid group followed by etherfication. Reduction of (*S*)-proline **294** using $LiAlH_4$ gave (*S*)-2-hydroxymethylpyrrolidine **295** in virtually quantitative yield, which was protected as its *N*-formyl derivative **296** by reaction with methylformate. Deprotonation of the alcohol using sodium hydride followed by alkylation with methyl iodide afforded the protected methyl ester **297**, which was subsequently deprotected with potassium hydroxide under refluxing conditions. Continuous extraction in a perforator with diethyl ether followed by evaporation and distillation gave **298** as a colourless liquid, which had all spectroscopic and optical rotation data identical to that reported.[138]



Scheme 86

Synthesis of (2'*S*)-1-(4,4-Dimethyl-5-*p*-tolyl-hex-5-enyl)-2'-methoxymethylpyrrolidine (286).

Incorporation of the chiral amine **298** onto the cyclisation precursor was accomplished following a similar procedure to that described in scheme 76. Initial attempts under refluxing conditions after 4 days in ethanol with 10 equivalents of sodium carbonate afforded the chiral aminobutyl styrene **286** in 58% yield (87% based on recovery). Furthermore, the yield and reaction time could be improved by carrying out the reaction in a sealed tube at 150°C for 2 days (77%). In comparison to the pyrrolidine system the increase in reaction time is presumably a consequence of steric hindrance. The product chiral aminoalkyl styrene was purified by column chromatography to afford a colourless oil, which correlated well with all the spectroscopic data (Scheme 87).



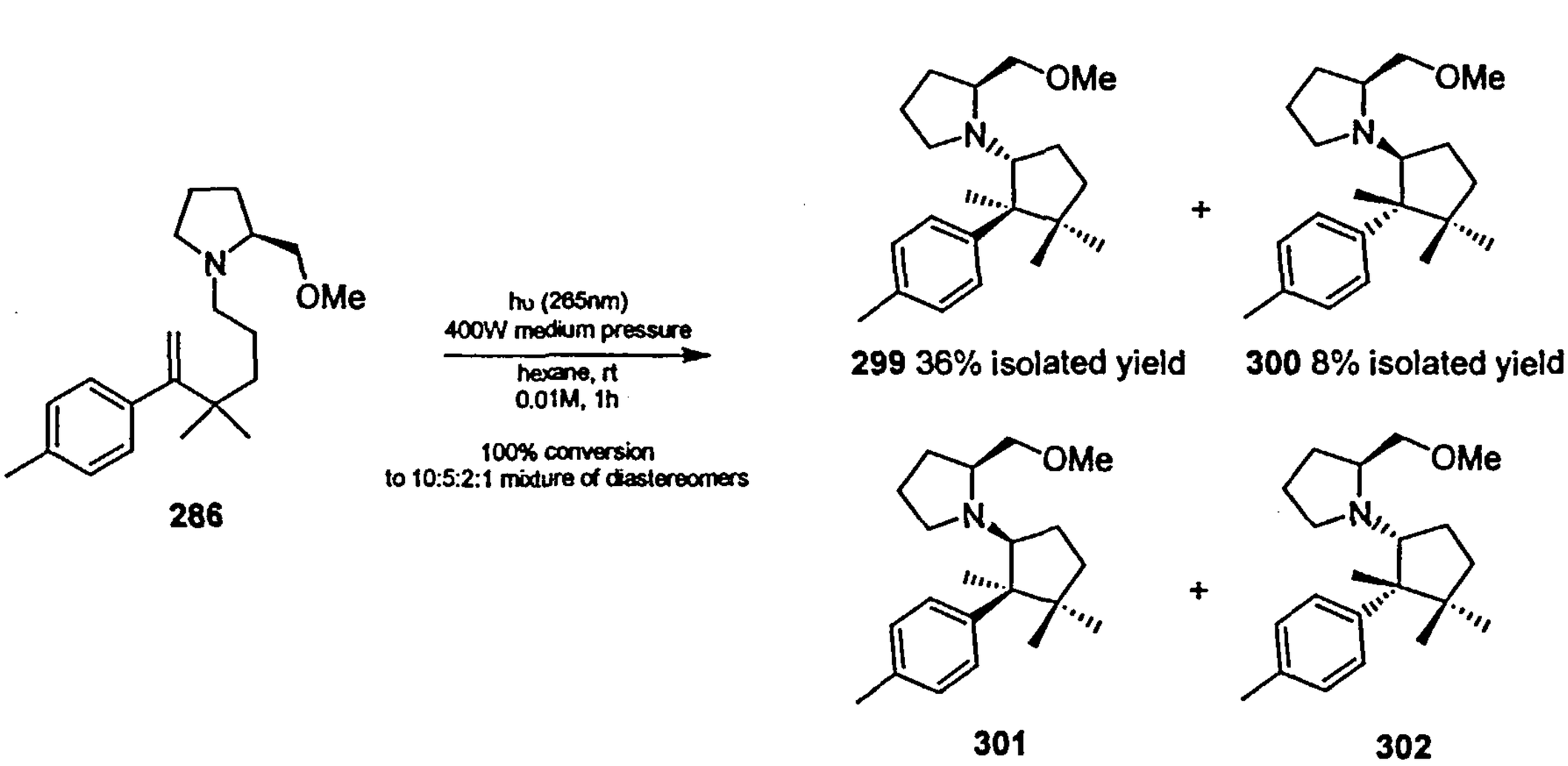
243 **286**

Scheme 87

With chiral photochemical precursor **286** at hand, the construction of the ring system via the critical photomediated cyclisation was employed, under similar conditions to that reported for the racemic syntheses of cuparene **1**.

Synthesis of (2'*S*, 1*R*, 2*S*)-2'-Methoxymethyl-1-(2, 3, 3-trimethyl-2-p-tolyl-cyclopentyl)-pyrrolidine (299) and (2'*S*, 1*S*, 2*R*)-2'-Methoxymethyl-1-(2, 3, 3-trimethyl-2-p-tolyl-cyclopentyl)-pyrrolidine (300).

Gratifyingly, irradiation of chiral aminobutyl styrene **286** in a hexane solution, carried out in a quartz vessel under a medium pressure mercury lamp also resulted in clean cyclisation. ^{1}H-NMR of the crude reaction mixture indicated the reaction to be 100% complete forming an approximate 10:5:2:1 ratio of possible diastereomers. The two major diastereomers **299** and **300** could be separated by careful column chromatography and revealed, by NOESY experiments to have the amine and aromatic ring *trans* to one another. The 5:1 ratio of *trans* to *cis* diastereomers was consistent with the results obtained by Lewis in the case of **219** (Scheme 49) and by ourselves for **239** (Scheme 77).

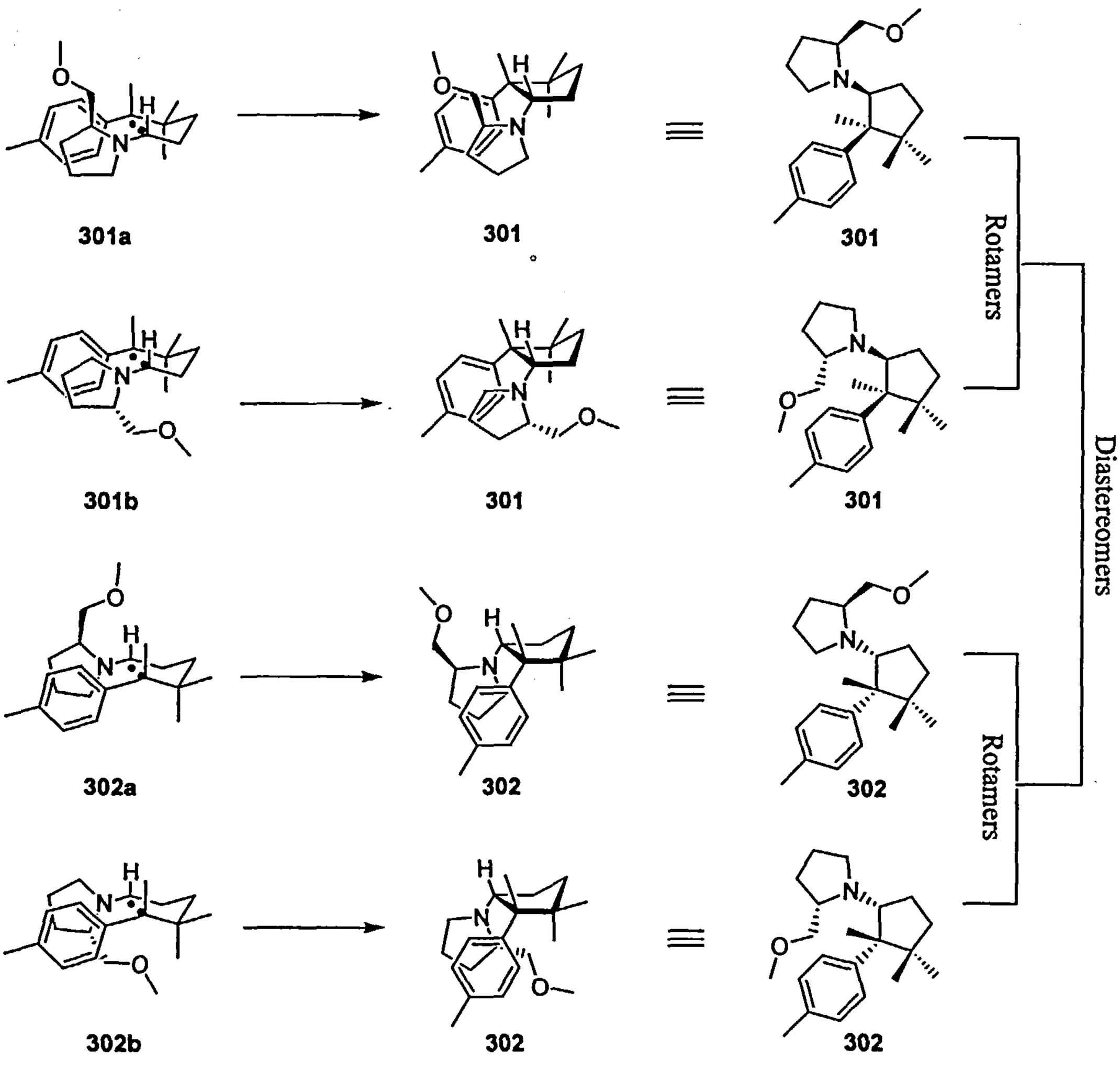


286

Scheme 88

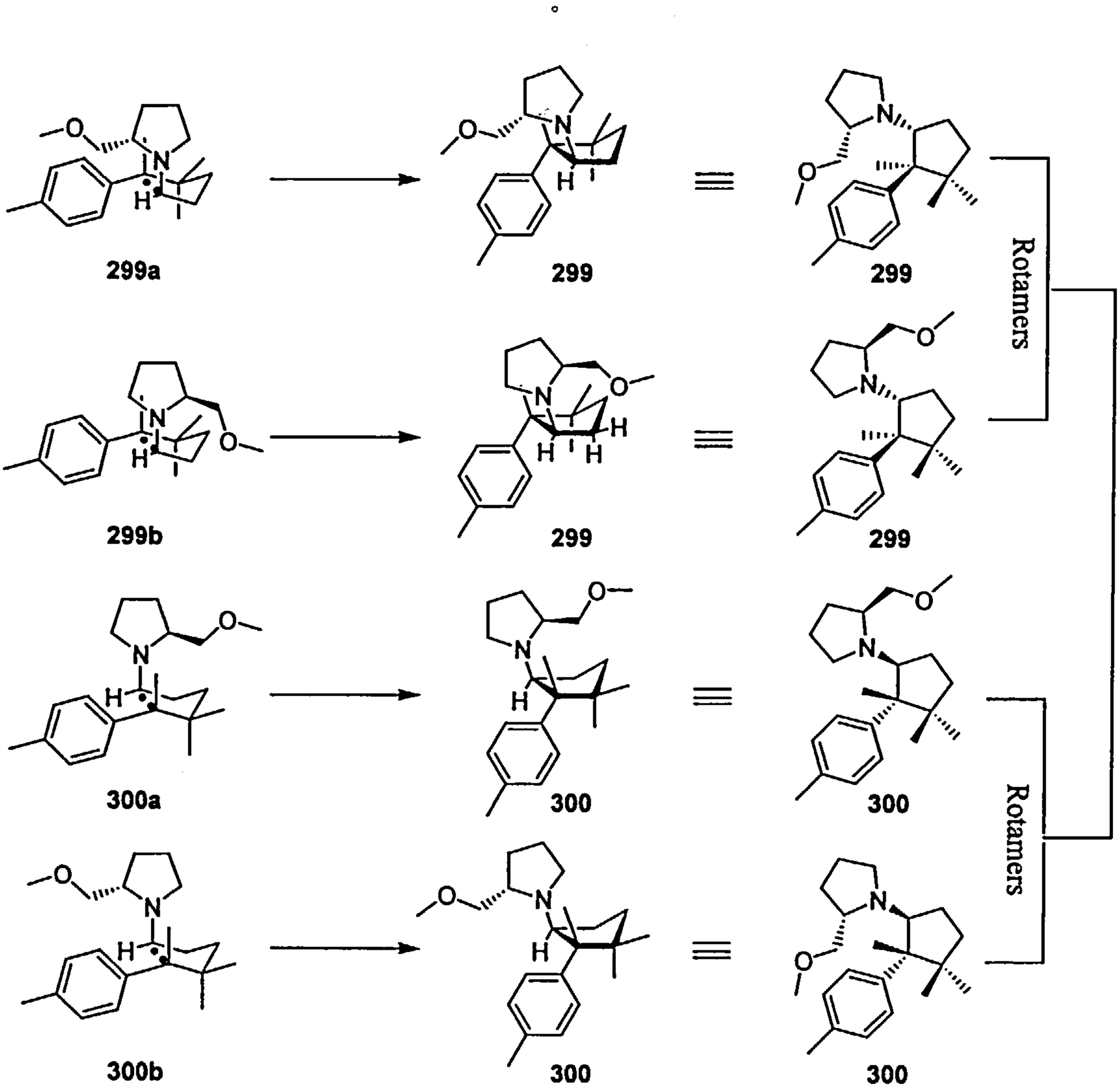
Product formation in favour of the *trans* substituted cyclopentane adducts **299** and **300** can reasonably be explained in terms of sterics, as indicated in scheme 88a. In the *cis*

case where the amine and aromatic ring are on the same side as in **301** and **302**, there is obvious unfavourable steric interaction between the amine auxiliary and aromatic ring. Also the rotamers **301a** and **302a**, which adopt a conformation where the CH_2OMe group of the auxiliary is pointing towards the aromatic ring seem to be less likely due to the increase in steric clash.



Scheme 88a

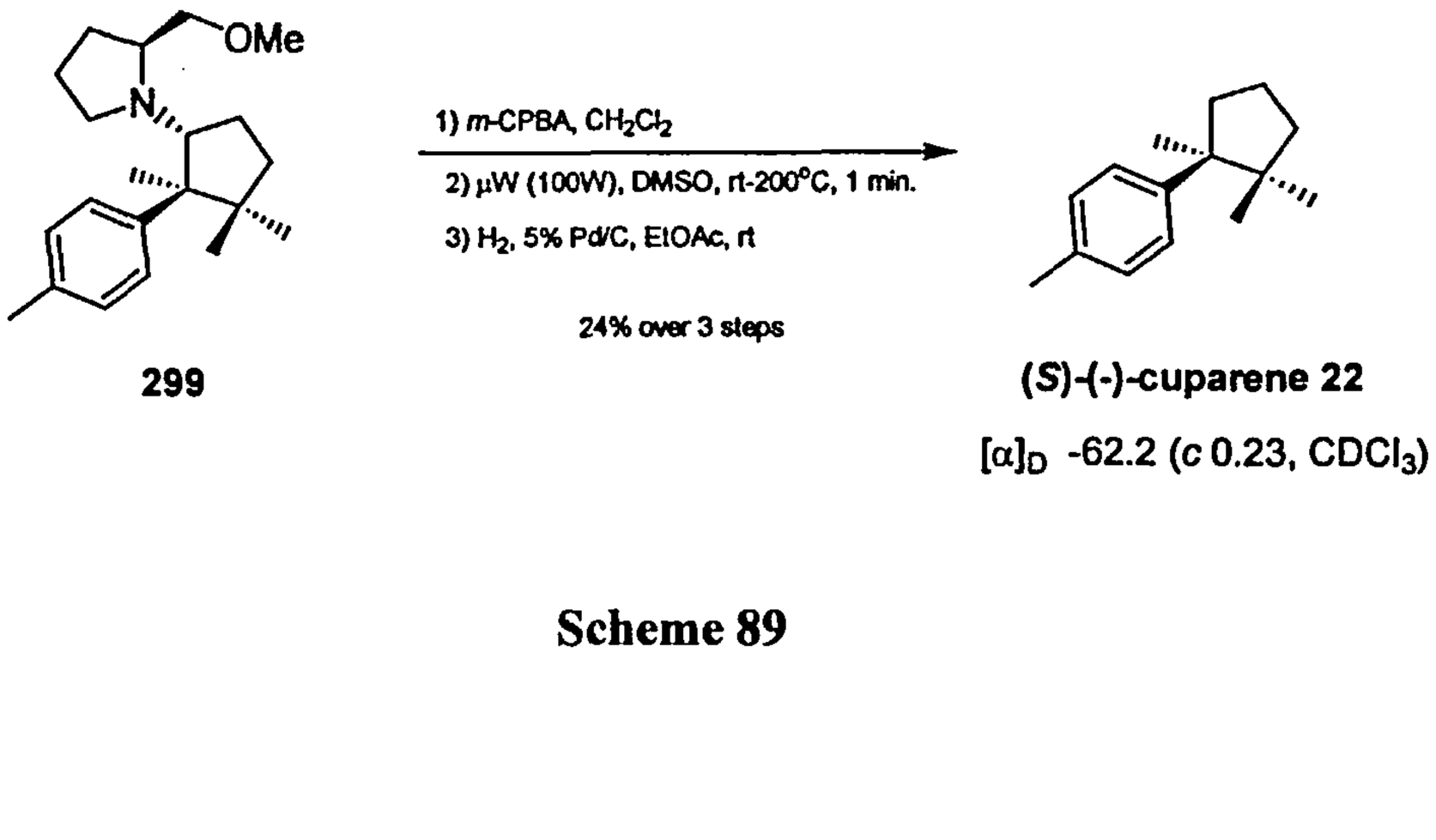
At present however, an explanation for the observed 2:1 selectivity between **299** and **300** is somewhat less obvious. As indicated in scheme 88b both diasteriomers **299** and **300** have two rotamers associated with them. Rotamers **299a** and **300a** seem to be least likely due to the unfavourable steric clash of the CH_2OMe group on the auxiliary during the radical-radical recombination step. The preference of **299b** over **300b** might be explained in terms of a greater electronic repulsion in **300b** between the electron rich aromatic ring and the lone pairs of the oxygen atom of the auxiliary. At present there appears to be little to differentiate between the two diastereomers thus resulting in surprisingly good selectivity.



Scheme 88b

In order to ascertain the absolute configuration of the newly created stereogenic centre in the major diastereomer **299**, the same three-step sequence developed in the racemic series was utilised to transform **299** to the natural product.

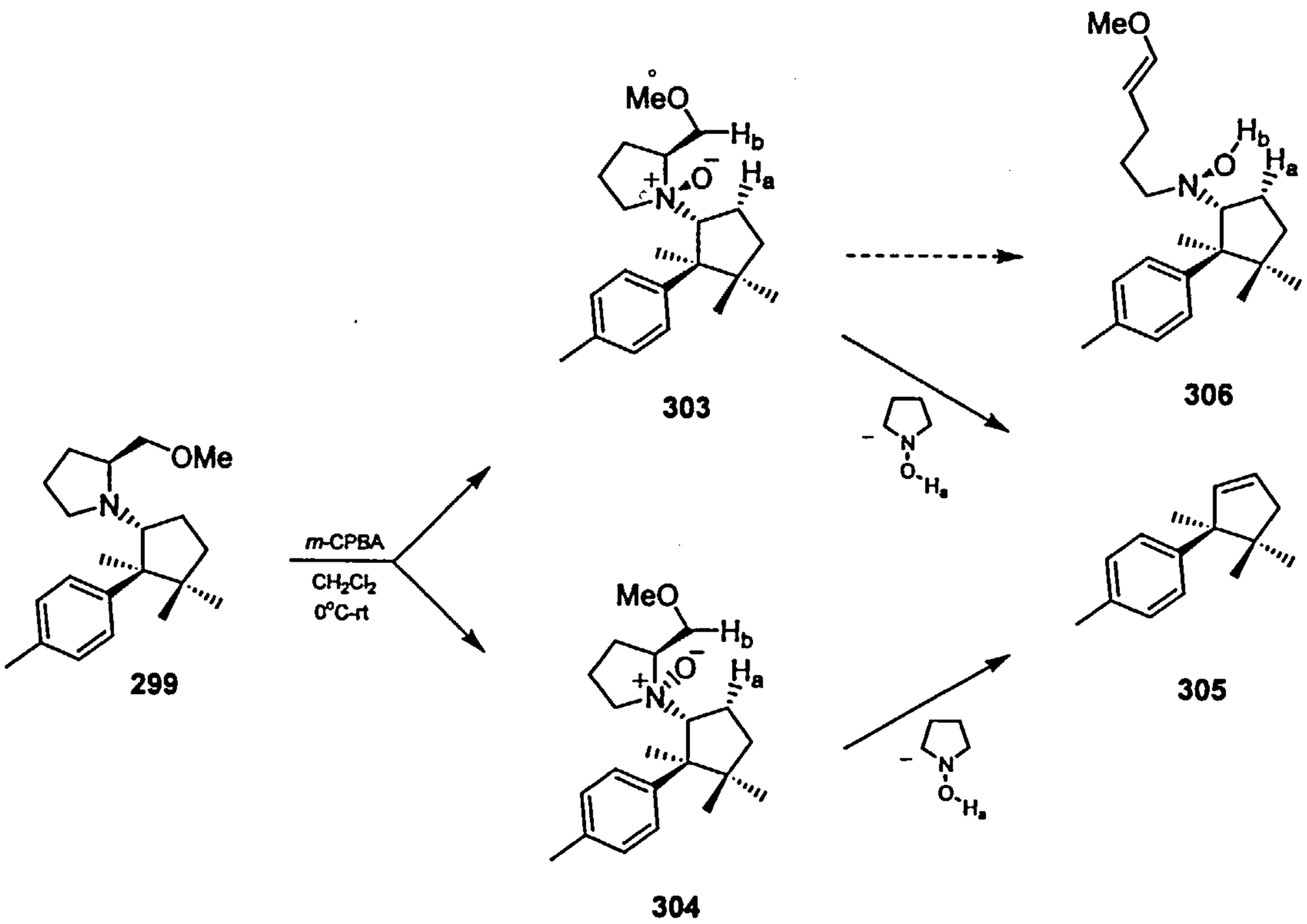
Oxidation of the major photocycloadduct **299** to the *N*-oxide could be achieved using *m*-CPBA in dichloromethane. The mixture of diastereomeric *N*-oxides were difficult to separate and were used directly for the subsequent transformation. Hence microwave assisted Cope elimination in DMSO and reduction of the double bond furnished (*S*)-(–)-cuparene **22** with an optical rotation identical to that reported in the literature ($[\alpha]_D$ –62.2, *c* 0.23, $CDCl_3$; lit. $[\alpha]^{20}_D$ –63 (*c* 1.6, $CHCl_3$),[139, 7d] thus establishing the absolute configuration of the major amine photoadduct **299**.



Scheme 89

It is noteworthy to mention that the thermally induced Cope elimination under standard conditions gave intractable mixtures of unidentifiable by-products with no sign of the product alkene by crude NMR. Although never isolated, the low/moderate yield of 24% obtained over the three steps can be attributed to a competing Cope elimination into the auxiliary. Oxidation of **299** to the *N*-oxide results in the formation of two diastereomers

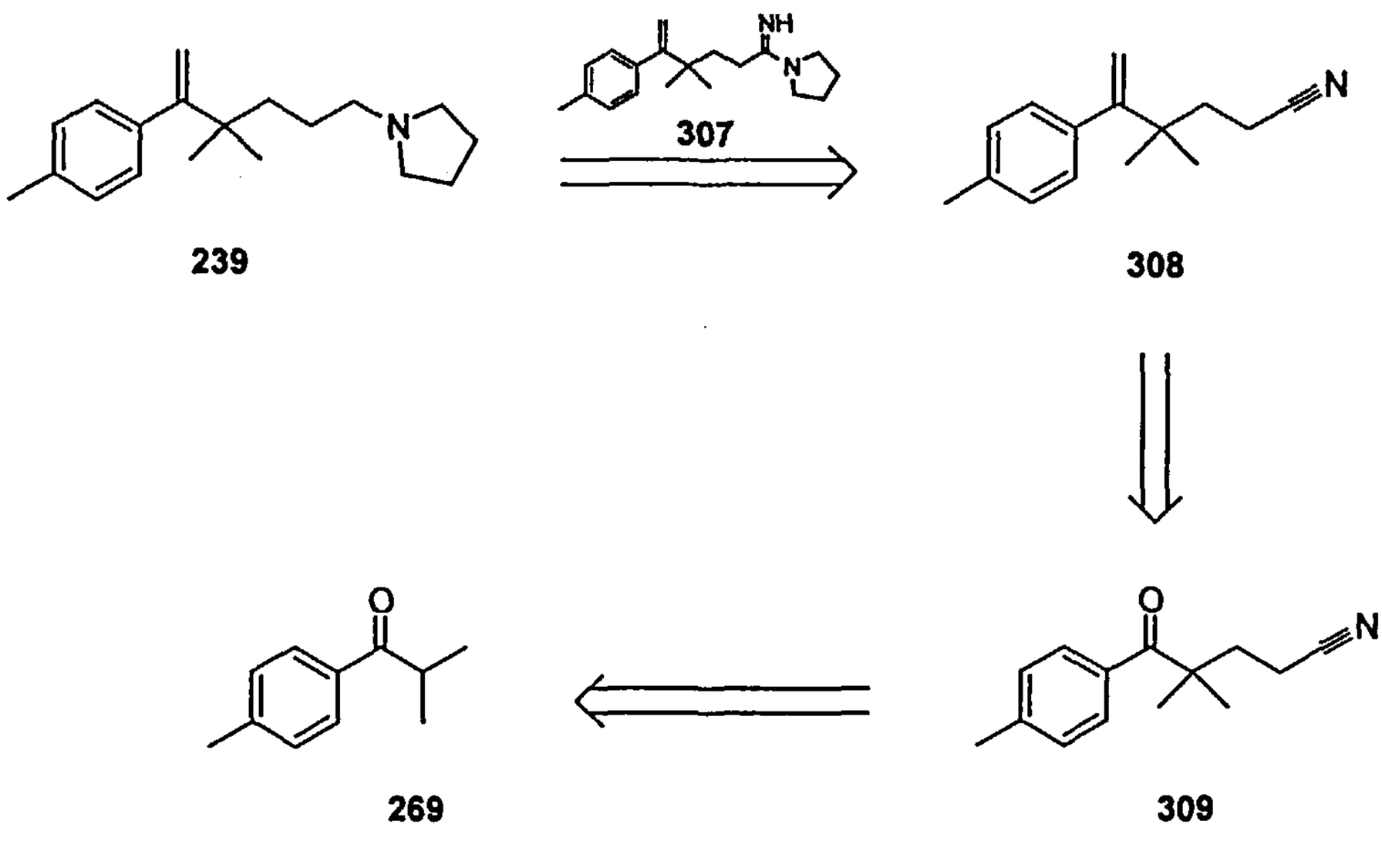
303 and **304**. Since it seems improbable that the β-H atom (H_b) on the auxiliary can achieve co-planarity with the *N*-oxide in **304**, Cope elimination on **304** should provide the desired product **305**. Conversely, the β-H atom (H_b) on the auxiliary of *N*-oxide **303** can achieve co-planarity in the planar transition state as shown in scheme 90 and therefore a competing Cope elimination into the auxiliary could also result to form ring opened product **306**, thus leading to the diminished yields observed for product alkene **305** (Scheme 90).



Scheme 90

2.5 Second-generation approach to photochemical precursor 239

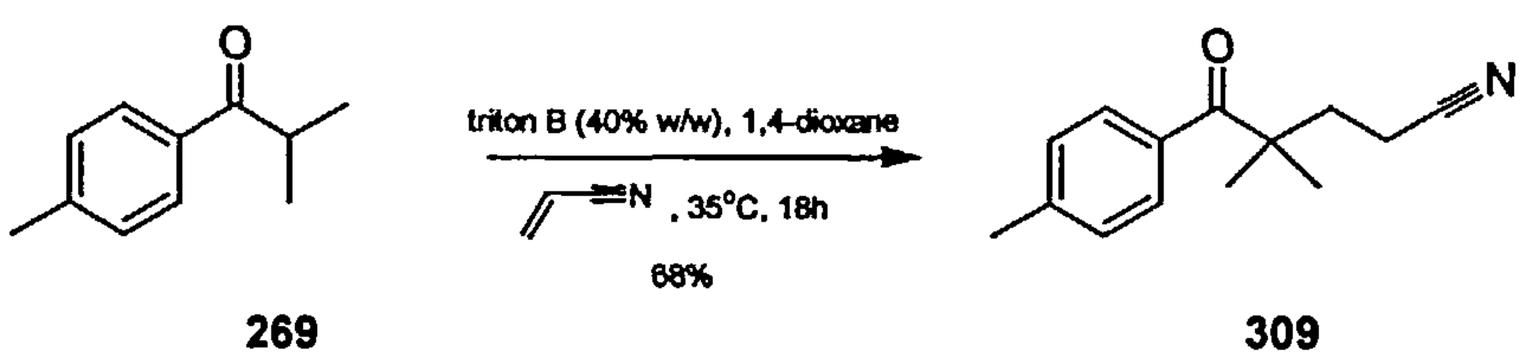
To streamline the synthetic sequence a more succinct route to aminoalkyl styrene **239** was deemed necessary. This led to the development of a second-generation approach to the synthesis of aminobutyl styrene **239**. It was envisaged that aminobutyl styrene **239** could be prepared from 4-methylisobutyrophenone **269** via a 3 step sequence, which involves conjugate addition to acrylonitrile to form the keto-nitrile **309**. Wittig reaction on the ketone functionality should furnish the alkene **308** without affecting the nitrile. Finally, a one-pot reductive amination on nitrile **308** should grant **239** via reduction of amidine intermediate **307** (Scheme 91).[140]



Scheme 91

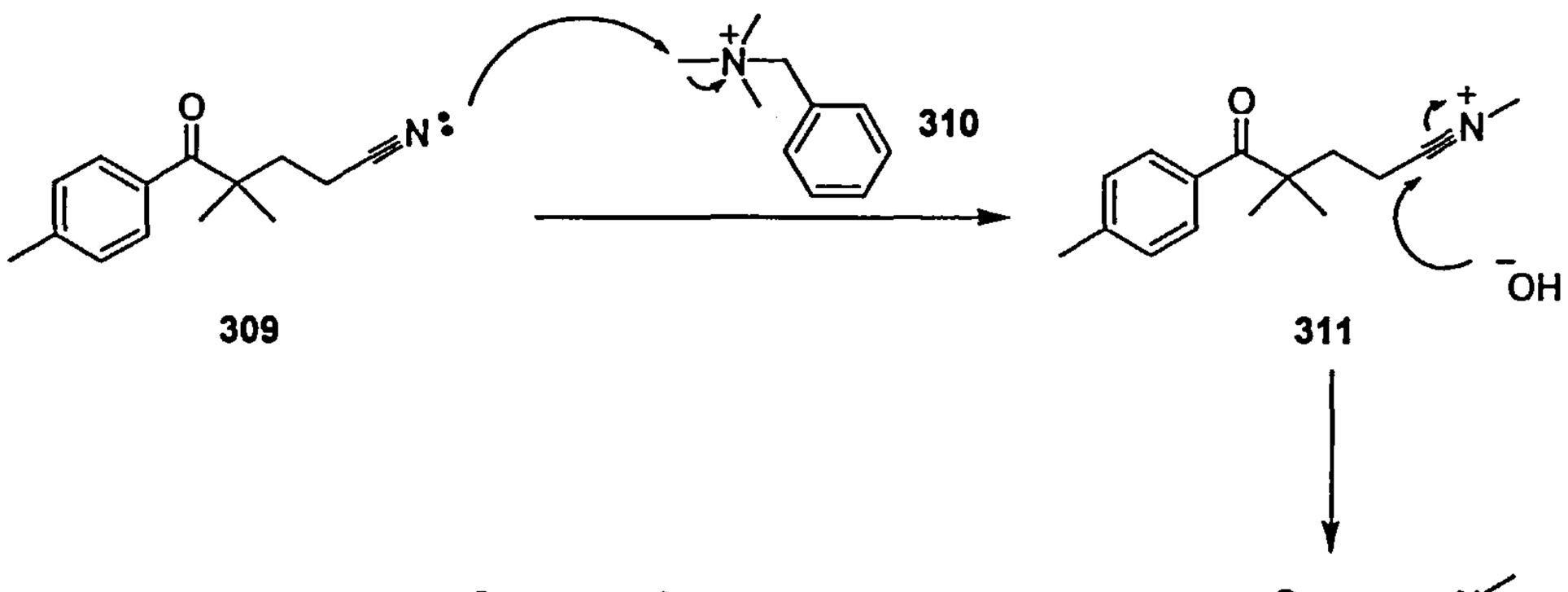
Synthesis of 4,4-Dimethyl-5-oxo-5-*p*-tolyl-pentane nitrile (309).

The synthesis of compound **309** was undertaken by adaptation of a literature procedure.[141] Cyanoethylation under biphasic conditions in the presence of catalytic benzyltrimethylammonium hydroxide (triton B) gave after acidic work-up the keto-nitrile **309** accompanied by trace amounts of a by-product. The product was separated by flash column chromatography to afford a colourless oil in 68% yield. The by-product has been tentatively assigned as amide **313** which could arise from nucleophilic attack of the product nitrile **309** onto the methyl moiety of benzyltrimethylammonium hydroxide to form intermediate **311**. Attack of a hydroxide anion onto **311** forms the aminal **312**, which tautomerises to amide **313** (Scheme 93).



269 309

Scheme 92



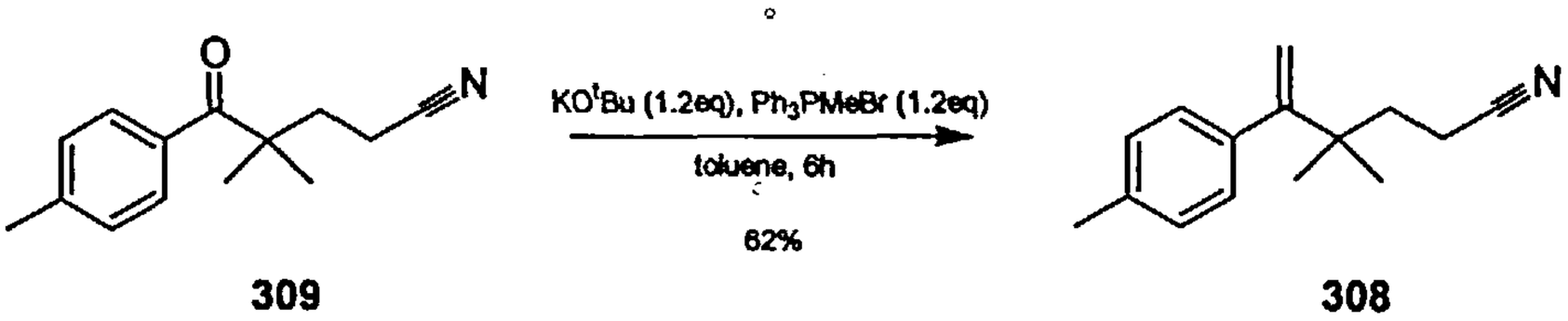
309 311

313 312

Scheme 93

Synthesis of 4,4-Dimethyl-5-p-tolyl-hex-5-enenitrile (308).

Wittig reaction on **309** utilising methyltriphenylphosphonium bromide and potassium *tert*-butoxide in toluene under refluxing conditions proceeded smoothly. A slight excess (1.2eq) of the two reagents was used to ensure complete formation of the alkylidenephosphorane. The by-product, eliminated triphenylphosphine oxide was isolated by cooling in hexane followed by filtration of the precipitate. Flash column chromatography of the crude product led to the nitrile **308** in 62% yield as a colourless liquid.

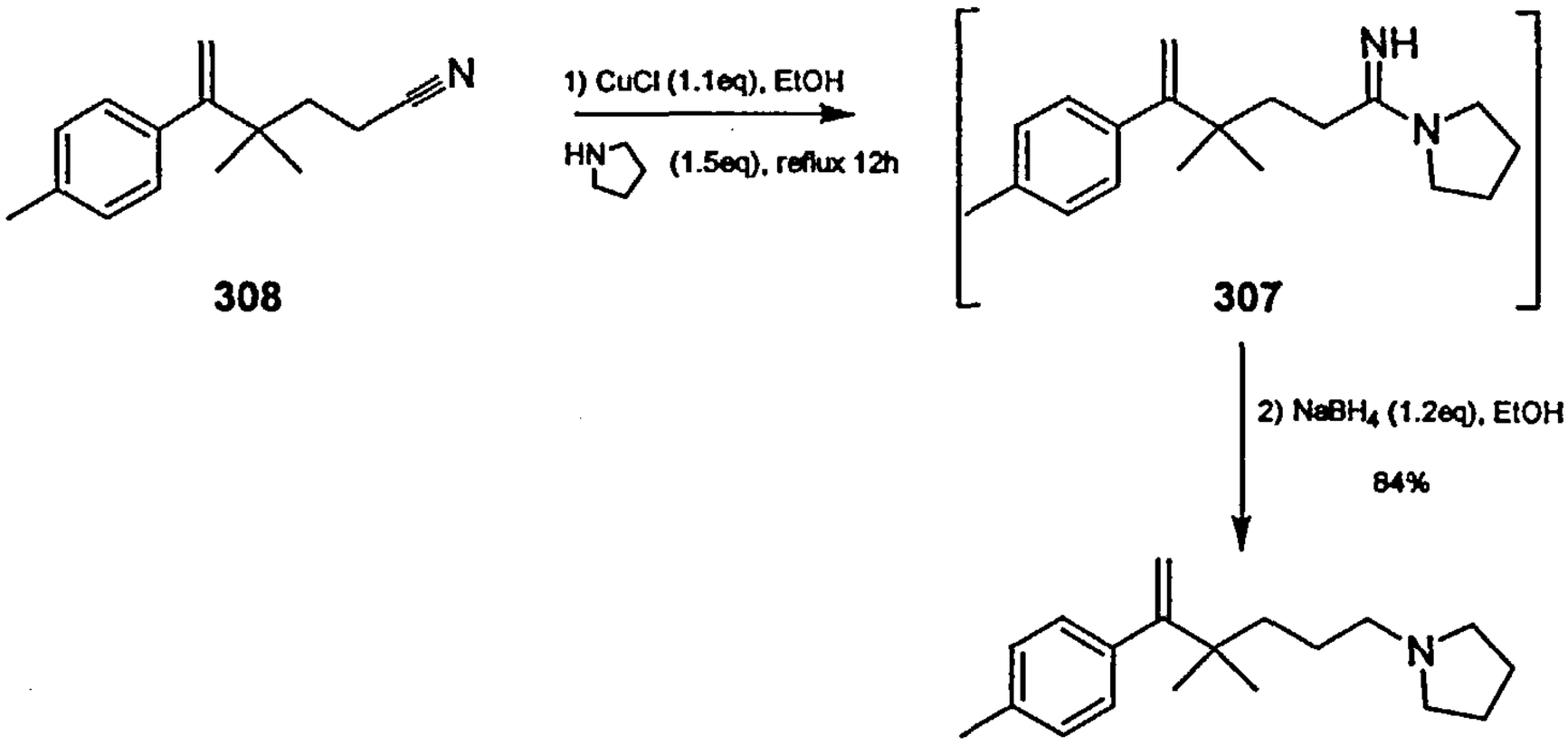


309 **308**

Scheme 94

Synthesis of 1-(4,4-Dimethyl-5-p-tolyl-hex-5-enyl)-pyrrolidine (239).

The conversion of nitrile **308** into the aminobutyl styrene **239** was accomplished using a modified Capdevielle procedure.[140] During the first step, copper (I) chloride was added to the nitrile in ethanol closely followed by the addition of pyrrolidine. The reaction was then refluxed for 12 hours and worked up to remove the copper salts. The resulting amidine **307**, was used without further purification and underwent $NaBH_4$ reduction to form the desired product **239** in 84% yield. In its broad outline, the mechanism is probably chelation of copper to the nitrile triple bond, which results in an increase in electrophilicity at the nitrile carbon, thus making it more susceptible to nucleophilic attack and forming key intermediate amidine **307**, which was then reduced (Scheme 95).



308 307

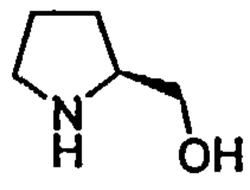
239

Scheme 95

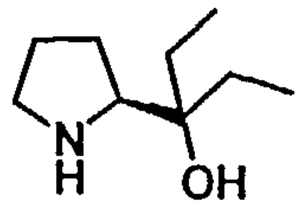
Although the reaction above proceeded favourably with pyrrolidine, using the auxiliary (*S*)-(+)-2-methoxymethylpyrrolidine **298** resulted in mainly starting material and other unidentifiable products which were difficult to isolate by column chromatography. Although not conclusive, this could be due to chelation of copper with the oxygen on the auxiliary rather than the nitrile triple bond. However, increasing the number of equivalents of copper (I) chloride made little difference. At this stage efforts were focussed on pursuing an auxiliary, which would both increase the level of selectivity in our photochemical cyclisation and limit the competing Cope elimination during removal.

2.6 Screening of chiral auxiliaries

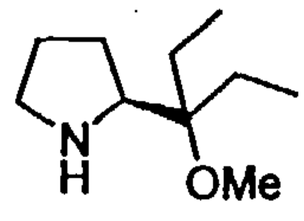
Initially, the syntheses of all the auxiliaries displayed in figure 9 below were targeted. (*S*)-2-Hydroxymethylpyrrolidine **295** was one of the intermediates in the synthesis to (*S*)-(+)-2-methoxymethylpyrrolidine **298** (Scheme 86) and was conveniently prepared from reduction of (*S*)-proline followed by purification by distillation (59%).



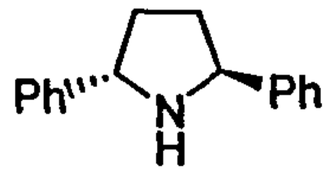
295



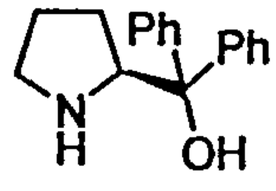
314



315



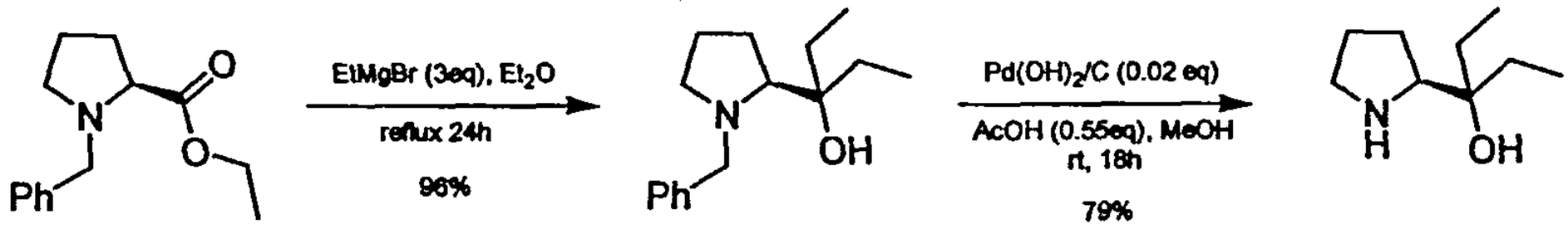
316



317

Figure 9

Auxiliaries **314** and **315**, which are protected at the β-position could be accessed via a modified procedure from commercially available *N*-benzyl-L-proline ethyl ester.[142] Reaction of the protected ethyl ester **318** with 3 equivalents of ethylmagnesium bromide ensued smoothly to afford the corresponding tertiary alcohol **319**. Subsequent work-up under acidic conditions gave a colourless oil which was purified by column chromatography to afford **319** in excellent 96% yield.

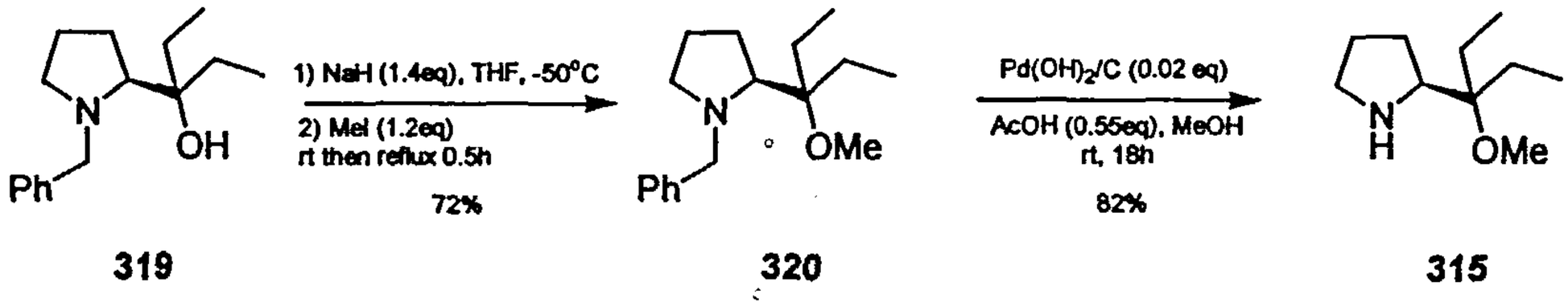


318 319 314

Scheme 96

Deprotection of the benzyl moiety was achieved via hydrogenolysis under atmospheric pressure in the presence of 10% $Pd(OH)_2$ and catalytic acetic acid.[143] Purification by kugelrohr distillation gave the amine **314** in 79% yield as colourless needles.

Additionally auxiliary **315** was also prepared from intermediate (*S*)-(–)-1-benzyl-2-(1-hydroxy-1-ethylpropyl)pyrrolidine **319**, through deprotonation of the alcohol using sodium hydride followed by alkylation with methyl iodide. The product was purified by column chromatography to give protected **320** as a colourless oil in 72% yield. Removal of the benzyl group was once more achieved *via* hydrogenolysis under the same conditions as described above in scheme 96, which furnished **315** in 82% yield as white needles (Scheme 97).



319 **320** **315**

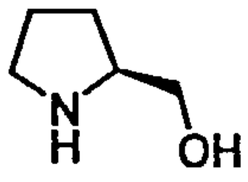
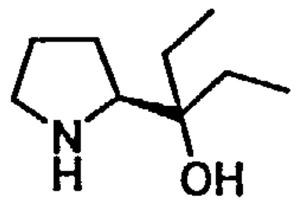
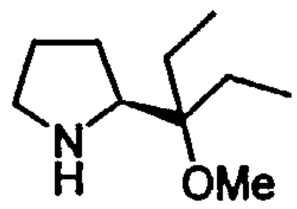
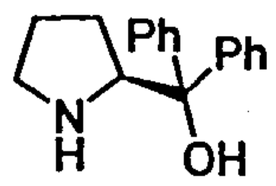
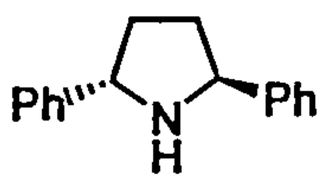
Scheme 97

Of particular interest was the C_2-symmetric diphenylpyrrolidine **316**, which looks attractive in this regard, both in terms of its proven effectiveness in a number of asymmetric processes[144] and the absence of any β-H's for competing Cope-elimination. However, its synthesis is non-trivial and required considerable time.[142, 145] In view of this and our time constraints we were fortunate to acquire a crude sample of **316** from Steel et al.[145] Diphenylprolinol **317** was inexpensive, commercially available and was used without further purification.

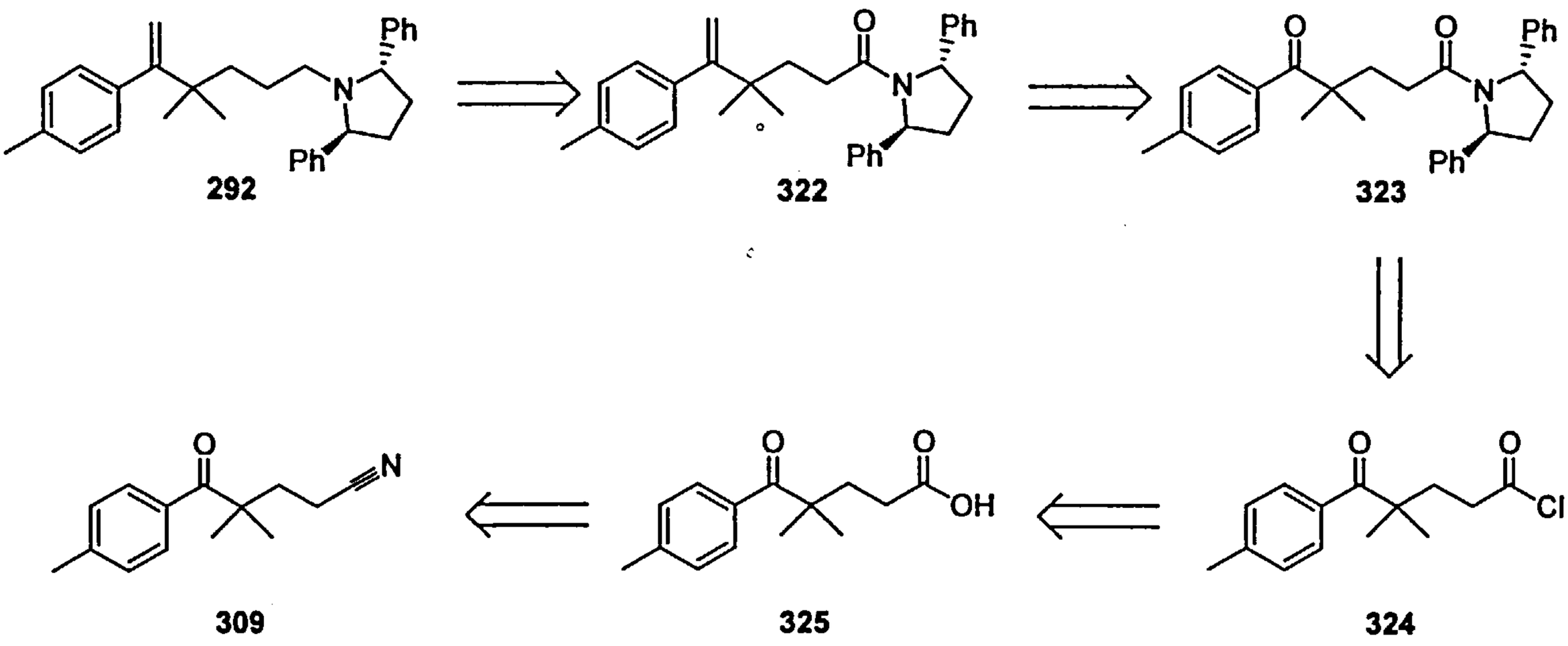
Coupling of **295, 314, 315** and **317** to alkyl bromide **243** was achieved in the usual manner, as summarised in the table 3 below. Unfortunately the C_2-symmetric diphenylpyrrolidine **316** failed to provide the desired product even under prolonged reaction conditions and higher temperatures in a sealed tube, resulting merely in

recovery of starting materials. Perhaps this might be due to its considerably more sterically encumbered nature.

Table 3: Coupling of auxiliaries to alkyl bromide **243.**

entry	reaction conditions	product	yield (%)	optical rotation $[a]_D^{25}$
	alkyl bromide (0.76eq) K_2CO_3(7.7eq) MeCN, reflux 3days.	**288**	78	-31.2 *c* 1.78, $CHCl_3$
	alkyl bromide (0.76eq) K_2CO_3(7.7eq) MeCN, reflux 4days.	**289**	74	-47.9 *c* 1.41, $CHCl_3$
	alkyl bromide (0.84eq) Na_2CO_3(8.4eq) EtOH, reflux 3days.	**287**	80	-45.7 *c* 1.29, $CHCl_3$
	alkyl bromide (0.76eq) K_2CO_3(7.7eq) MeCN, reflux 4days.	**290**	76	28.9 *c* 1.39, $CHCl_3$
	1) alkyl bromide (0.77eq) KHMDS (1.2eq), THF, -78°C-rt then reflux 18h.	**SM**	-	-
	2) alkyl bromide (0.76eq) Na_2CO_3 (7.7eq) EtOH, reflux 1week	**SM**	-	-
	3) alkyl bromide (0.76eq) Na_2CO_3(7.7eq), EtOH 150°C sealed tube.	**SM**	-	-

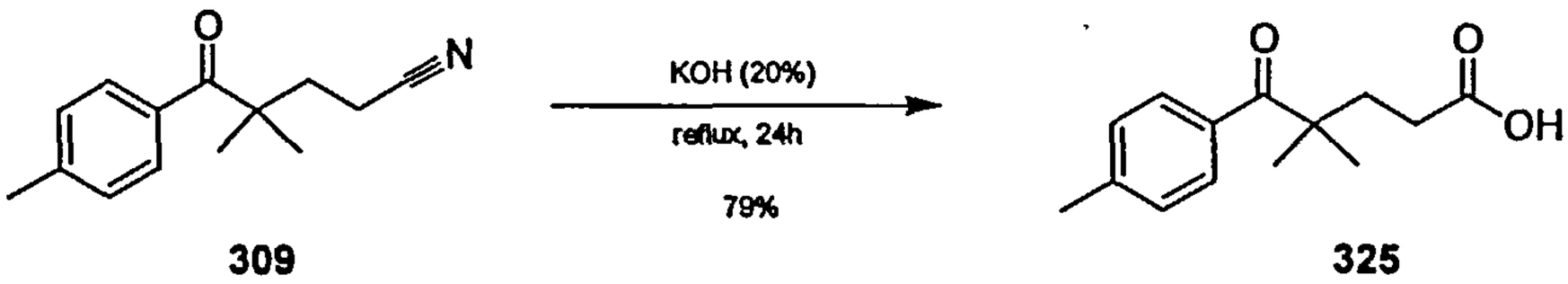
To circumvent this lack of reactivity a new retrosynthesis of **292** was considered, exploiting the keto-nitrile **309**. Hydrolysis of previously prepared **309** should form the keto-acid **325**, which could be converted to the reactive acid chloride **324**. Reaction of **324** with our C_2-symmetric diphenylpyrrolidine **316** should secure the amide **323**. It was anticipated that subsequent Wittig reaction would generate the amide **322**. Finally, $LiAlH_4$ reduction on amide **322** would complete the synthesis of **292** (Scheme 98).



Scheme 98

In view of the expense and difficulty in obtaining our C_2-symmetric auxiliary **316**, it was decided to evaluate this approach using dibenzylamine **326.**

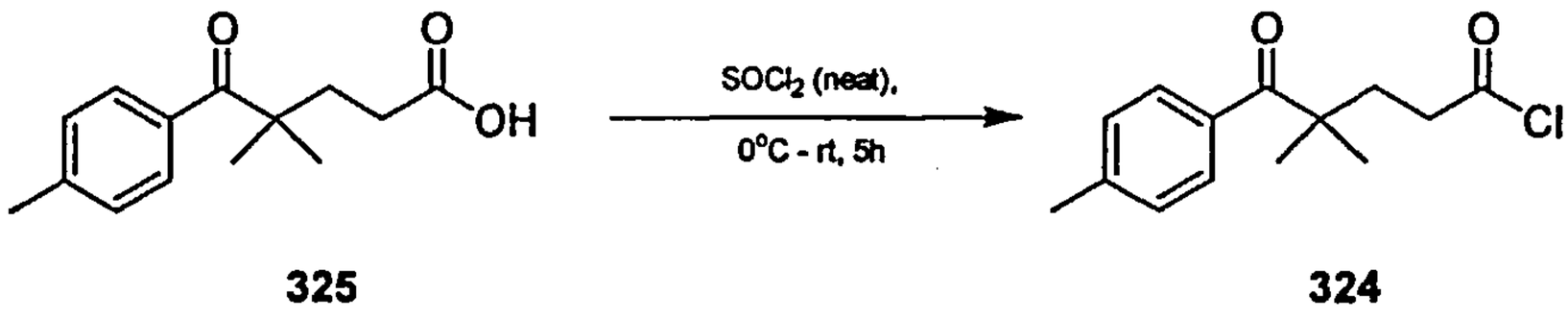
Hydrolysis of **309** under refluxing aqueous basic conditions proceeded smoothly, following an effective literature procedure.[146] The resultant acid **325** was recrystalised from hexane/toluene and gave white needle like crystals upon standing in 79% yield.



309 **325**

Scheme 99

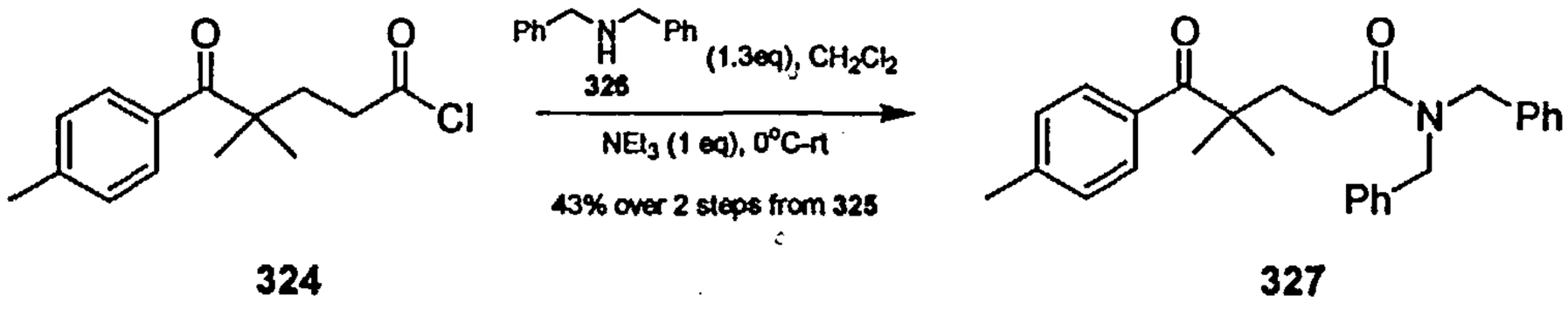
A number of different procedures are available for the conversion of carboxylic acids to acid chlorides. Initial work showed that refluxing in thionyl chloride in various organic solvents, with or without activation by dimethylformamide, yielded only intractable mixtures. However, it was found that simple reflux in neat thionyl chloride gave good preparative yields of acid chloride **324**, which was sufficiently pure by NMR to be used in the next step without further purification (Scheme 100).



325 **324**

Scheme 100

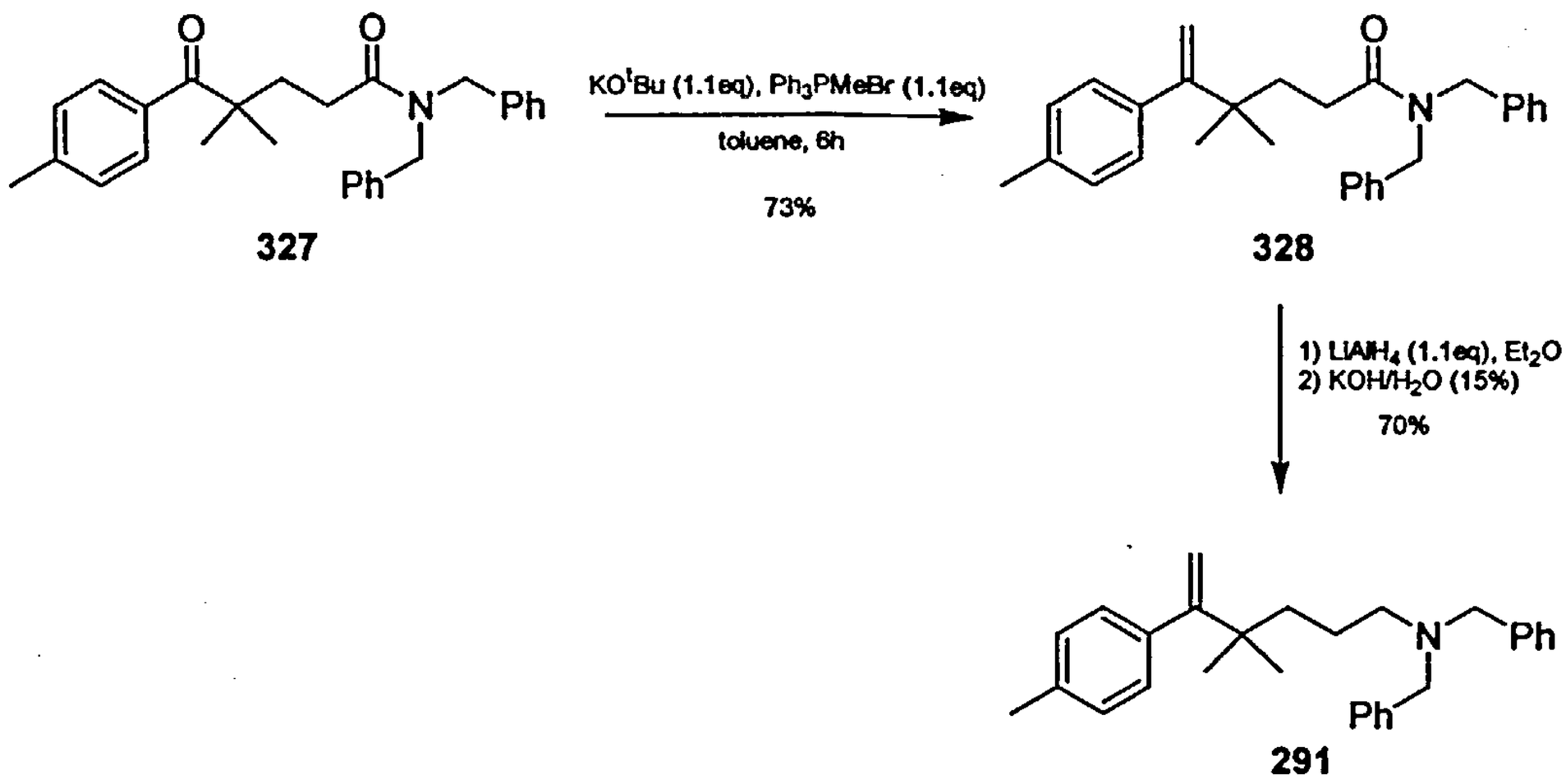
Amination of acid chloride **324** was achieved using a modification to Bertrand's procedure.[147] Treatment of **324** with dibenzylamine in dichloromethane in the presence of triethylamine gave the amide **327** as a yellow oil, after purification by column chromatography. During the addition of triethylamine at 0°C the reaction turns orange initially and progressively turns dark brown over time indicating decomposition. However, the yield of 43% over the two steps from **325** was sufficient at this stage and no further attempts were made to optimise the process (Scheme 101).



324 **327**

Scheme 101

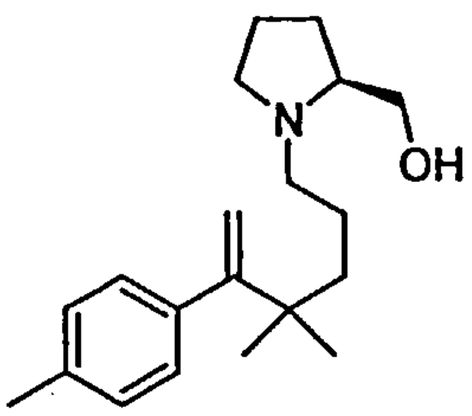
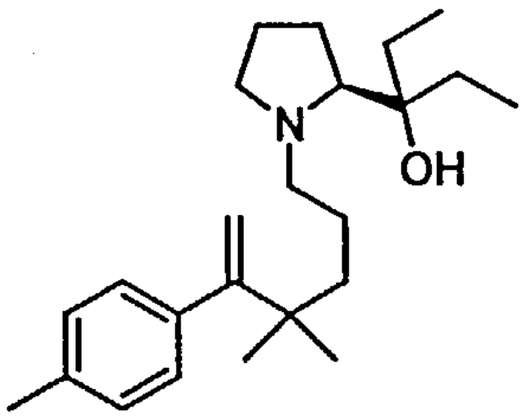
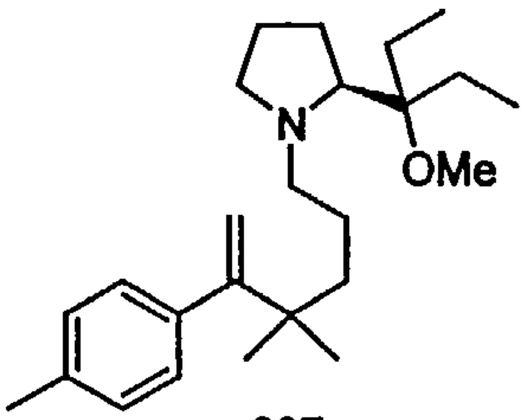
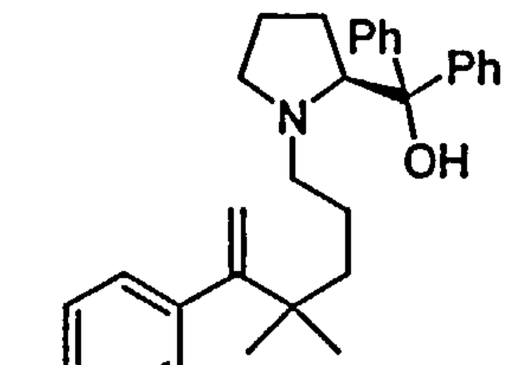
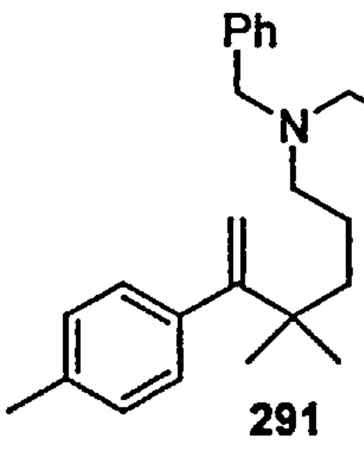
Wittig reaction on **327** using similar conditions to that in scheme 94 afforded the desired amide **328** in 73% yield as a pale yellow oil following purification. The product was characterised by IR, ^{1}H NMR, ^{13}C NMR and low-resolution mass spectra and was in accordance with expectations. Finally, $LiAlH_4$ reduction in dry diethyl ether on amide **328** gave requisite amine **291** in 70% yield as a colourless oil after purification (Scheme 102).



Scheme 102

In view of previous findings, it was anticipated that all the aminoalkyl styrenes synthesised above would undergo intramolecular photochemical reactions to form cyclisation products. However, disappointingly all attempts to realise this plan met with failure. Irradiation under a variety of reaction conditions exemplified in table 4 below resulted invariably in polymerisation and decomposition products.

Table 4: Photo-irradiation results.

compound	solvent	λ_{max} (nm)	time	product yield (%)
 **288**	hexane	medium pressure	0.5h	intractable mixtures
	hexane	medium pressure	1h	polymerisation
 **289**	hexane	medium pressure	15mins	intractable mixture
	hexane	medium pressure	0.5h	polymerisation
	hexane	medium pressure	1h	polymerisation
 **287**	hexane	medium pressure	20mins	decomposition
	hexane	low pressure	20mins	intractable mixtures
	hexane	low pressure	3h	decomposition
 **290**	hexane	medium pressure	0.5h	polymerisation
	hexane	low pressure	0.5h	polymerisation
 **291**	hexane	medium pressure	0.5h	polymerisation
	hexane	medium pressure	15mins	polymerisation
	hexane	low pressure	0.5h	polymerisation

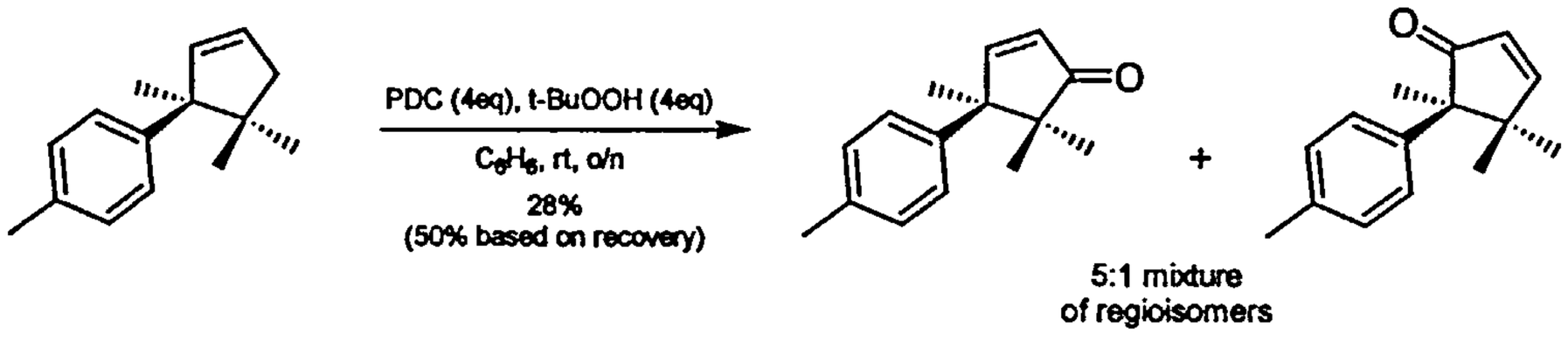
At present, the reason for this is not obvious. The NMR's obtained were unclear with no evidence of the required products and upon prolonged irradiation became progressively more complicated. The failure of **287** to produce any cyclisation adduct was most surprising since it differs with **286** in only an additional geminal diethyl group at the β-position. Although not yet conclusive, the geminal diethyl groups at the β-position might prevent maximum orbital overlap and coulombic attraction in the lowest energy folded conformation of the singlet exciplex. This could inhibit the regioselective 1,6-proton transfer step to occur via a least motion pathway.

Independent ultra-violet studies on the free amines **316** and **326** indicate a large absorption between (254-265nm), which overlaps at the wavelength absorbed by the styrene. This could be contributing to the observed outcome since the excited singlet state could be quenched by SET from the pendent phenyl donor groups on the amine. Consequently, at this late stage no further experiments were attempted in order to understand these unusual results. However, this work is still in progress in the Grainger laboratory and will be looked at in more detail.

2.7 Synthesis of (±)-α-and γ-cuparenone (331 and 332)

In parallel to this work, the synthesis of other members of the cuparene class of sesquiterpenes was explored. Further elaboration of the double bond in **283**, the precursor to (±)-cuparene **1**, enabled a synthesis of (±)-cuparenone as a mixture of α- and γ-isomers (**331** and **332**) via allylic oxidation[148] followed by reduction of the double bond.

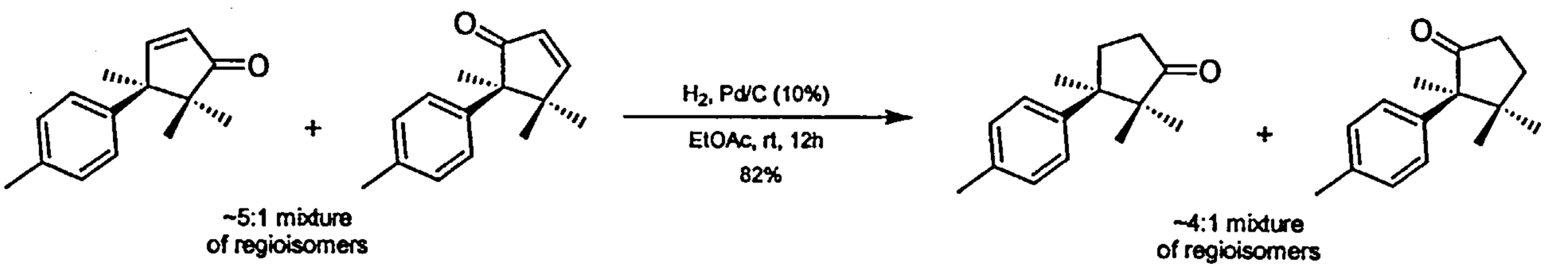
Allylic oxidation on **283** was achieved using *tert*-butylhydroperoxide and pyridinium dichromate in a 1:1 molar ratio in benzene. Careful column chromatography of the crude reaction mixture gave an inseparable mixture of regioisomers **329** and **330** in a 5:1 ratio by NMR. Thin layer chromatography indicated one spot under uv and the major isomer **329** was assigned based on literature precedent (Scheme 103).[21, 32]



283 **329** **330**

Scheme 103

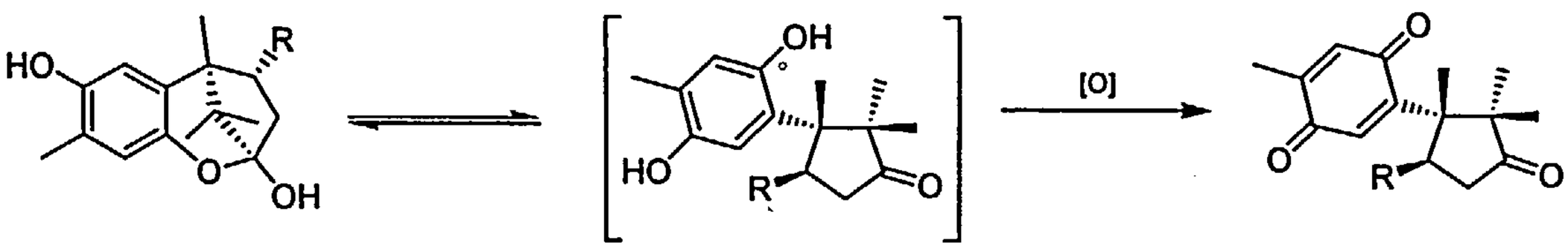
Hydrogenation of the double bond in **329** and **330** was accomplished under standard conditions at atmospheric pressure. The products were inseparable by column chromatography and gave a 4:1 mixture of regioisomers. The major isomer **331** was assigned as (±)-α-cuparenone based on literature precedent.[21, 32]



Scheme 104

2.8 Synthesis towards enokipodin A, B, C and D

Antimicrobial cuparene-type of sesquiterpenes the enokipodins, another series of natural products, could also be accessible utilizing this methodology. Enokipodins A, B, C and D have recently been isolated[149] from the culture medium of an edible mushroom, *Flammulina veluptipes* and have attracted attention as synthetic targets due to their antibacterial activity against gram-positive bacteria (Scheme 105).[149]

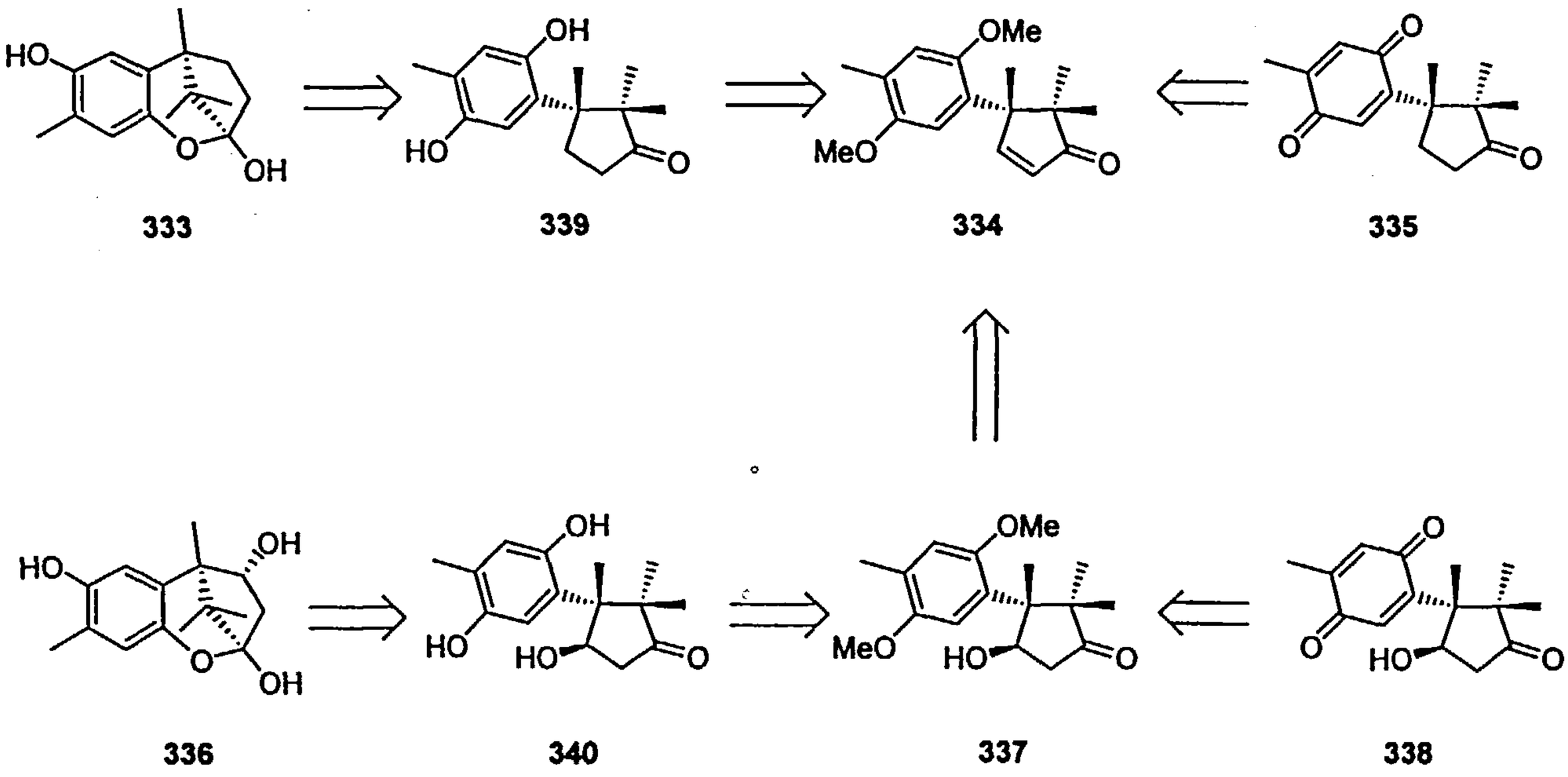


333 R=H (enokipodin A) **334** R=H **335** R=H (enokipodin B)

336 R=OH (enokipodin C) **337** R=OH **338** R=OH (enokipodin D)

Scheme 105

It was envisaged that all four sesquiterpenes **333, 335, 336** and **338** could be accessible from key intermediate **334**, since the free phenolic hydroxyl groups are in equilibrium with the hemiketals **333** and **336.**

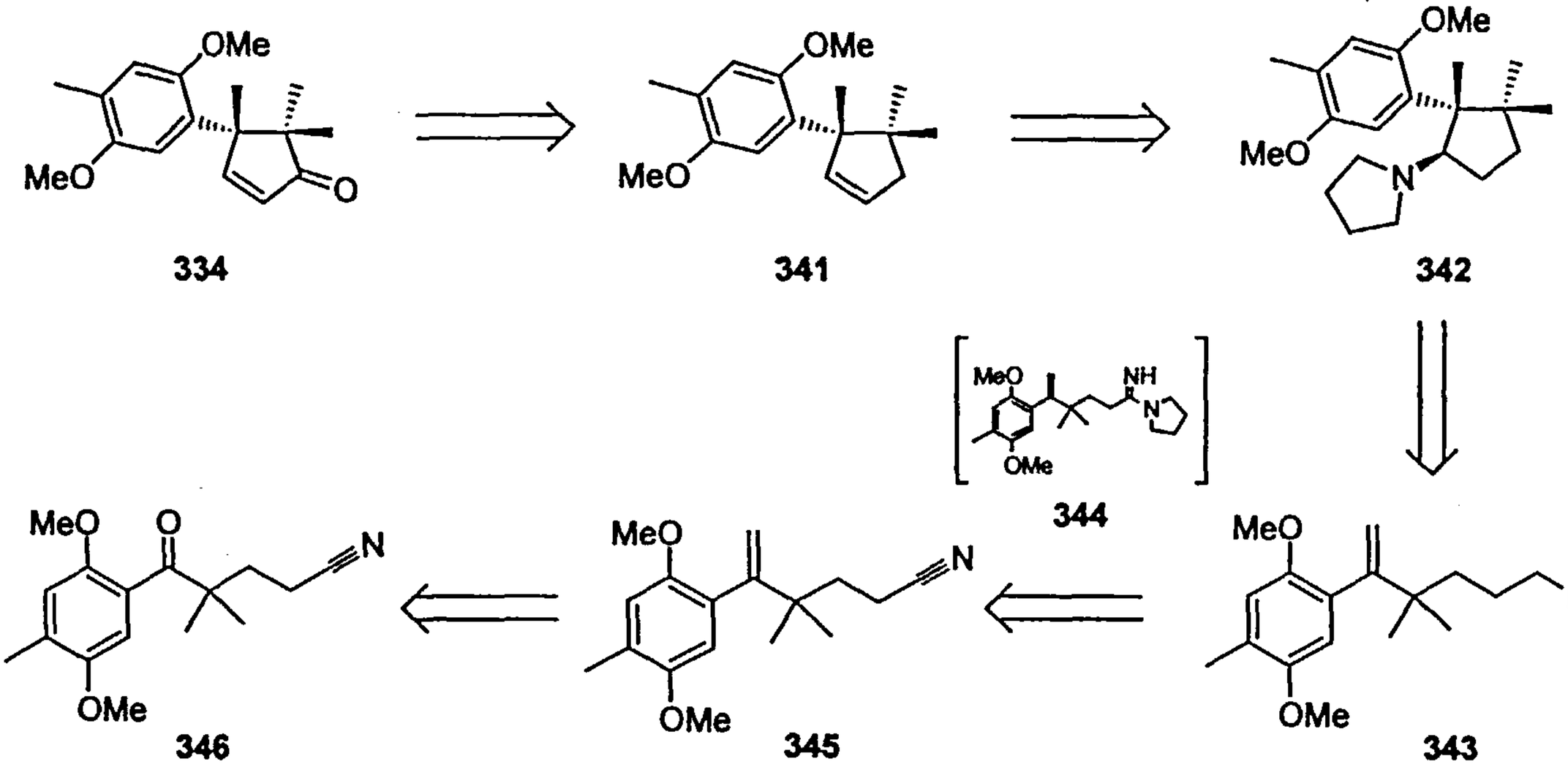


333 **339** **334** **335**

336 **340** **337** **338**

Scheme 106

Thus, hydrogenation of the double bond in **334** followed by oxidation of the aromatic ring should lead to the quinone **335.** Alternatively, hydrogenation followed by deprotection of the methoxy groups on the aromatic ring to form phenolic hydroxyl moieties should give **339**, which is in equilibrium with the hemiketal **333.** Conversely, epoxidation of the double bond in **334**, which should proceed from the opposite side of the aromatic ring followed by regioselective ring opening adjacent to the carbonyl functionality should provide **337.** Finally, regioselective oxidation of the aromatic ring should provide **338**, alternatively deprotection of the methoxy groups to hydroxyl moiety **340** should allow for the formation of the hemiketal **336** (Scheme 106).

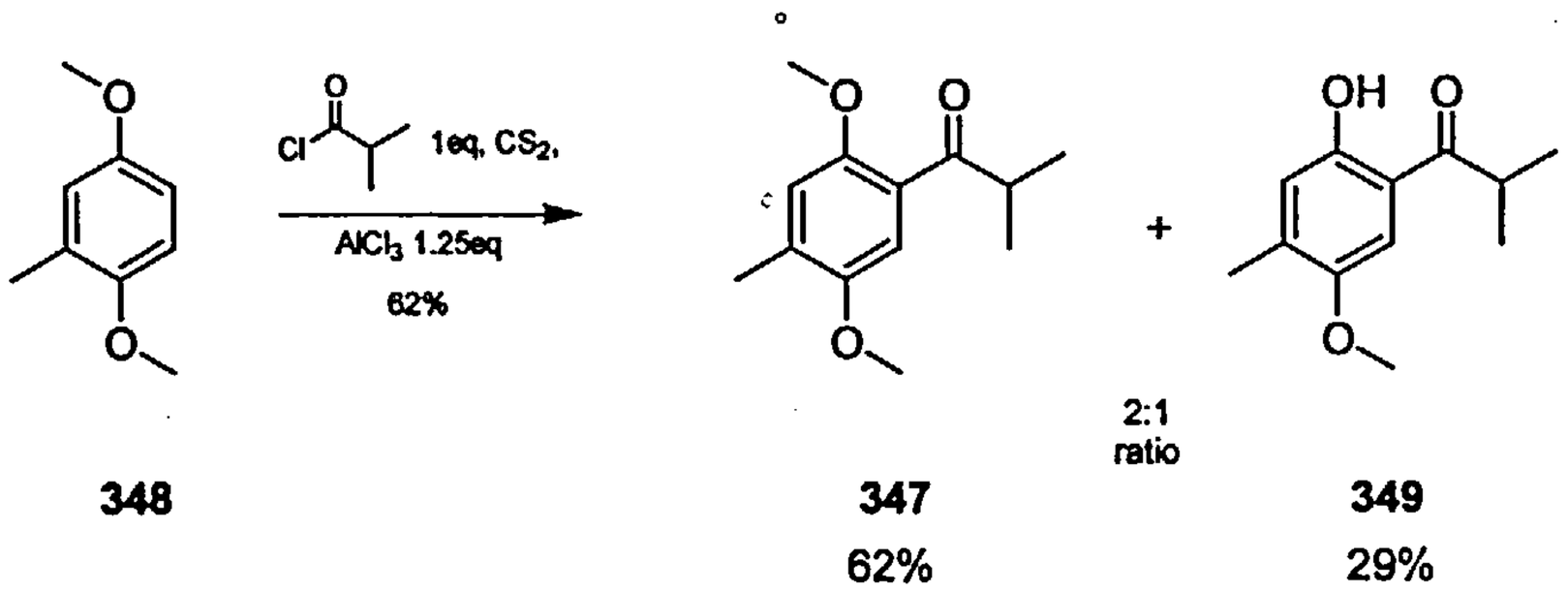


Scheme 107

A search in the literature showed that 2,5-dimethoxy-4-methylisobutyrophenone **347** is known and can be prepared via a regioselective Friedel-Crafts acylation. The photochemical precursor **343** required to test the cyclisation could be prepared from **347** via a three step sequence involving conjugate addition to acrylonitrile to form keto-nitrile **346,** Wittig reaction and a one-pot reductive amination of nitrile **345** via an amidine intermediate **344.** A photomediated cyclisation on **343,** under similar conditions to that employed in scheme 88 should provide after separation the cyclised amine adduct **342.** Cope elimination on the amine oxide of **342** and subsequent allylic oxidation on cyclised alkene **341** should provide the key intermediate α,β-unsaturated ketone **334** required for the synthesis of all four sesquiterpenes **333, 335, 336** and **338.**

Synthesis of 1-(2', 5'-Dimethoxy-4'-methyl-phenyl)-2-methyl-propan-1-one (347).

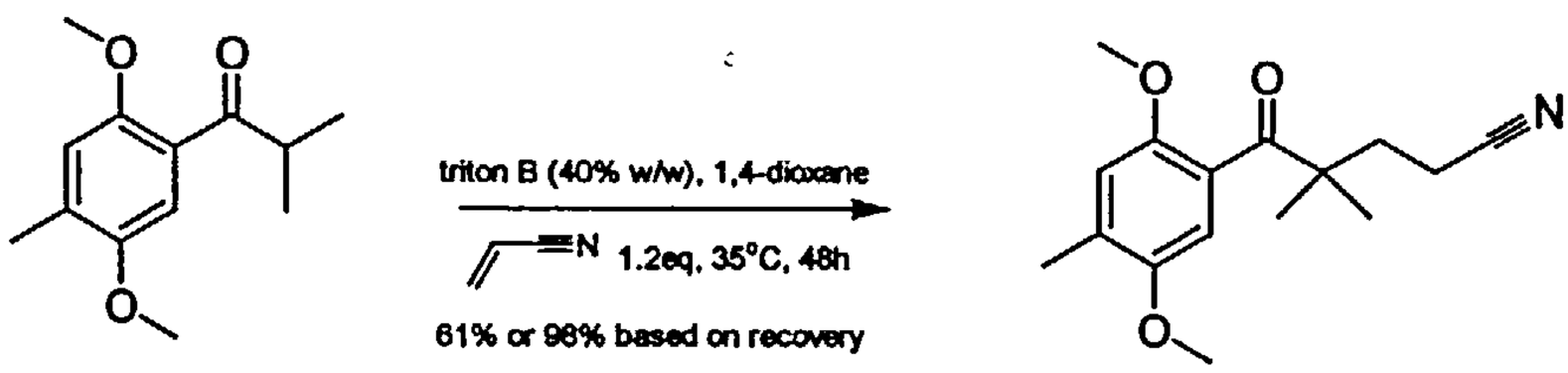
The synthesis of compound **347** was undertaken by adaptation of a literature procedure.[150] Regioselective Friedel Crafts acylation on 2,5-dimethoxytoluene **348**, in carbon disulphide at room temperature afforded a 2:1 ratio of products. The major product was isolated by careful column chromatography in 62% yield and gave spectroscopic data identical to that reported in the literature.[151] The minor product was isolated and tentatively assigned as phenol **349**, which had undergone deprotection of one of the methoxy groups on the aromatic ring.



Scheme 108

Synthesis of 5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-5-oxo-pentanenitrile (346).

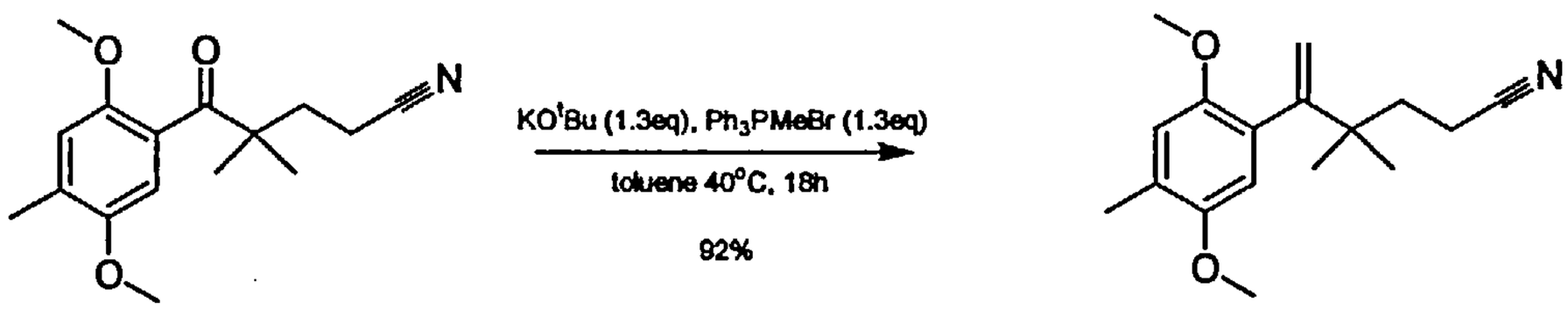
Cyanoethylation under biphasic conditions in the presence of catalytic benzyltrimethylammonium hydroxide gave after acidic work-up the keto-nitrile **346**. There was no sign of any by-products and the product was purified by flash column chromatography to afford the keto-nitrile **346** in 61% yield, or 98% based on recovery. The product was fully characterised and gave spectroscopic data consistent with expectations (^{1}H NMR, ^{13}C NMR and low and high-resolution mass spectra) (Scheme 109).



Scheme 109

Synthesis of 5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-hex-5-enenitrile (345).

Wittig reaction on **346** utilising methyltriphenylphosphonium bromide and potassium *tert*-butoxide in toluene under refluxing conditions proceeded smoothly. Again, the by-product, eliminated triphenylphosphine oxide, was isolated by cooling in hexane followed by filtration of the precipitate. The product was purified by flash column chromatography to afford the alkene **345** as a colourless oil in a surprising 92% yield. The higher yield of 92% compared to 62% for compound **308** achieved in the cuparene synthesis (scheme 94) is unclear at present (Scheme 110).

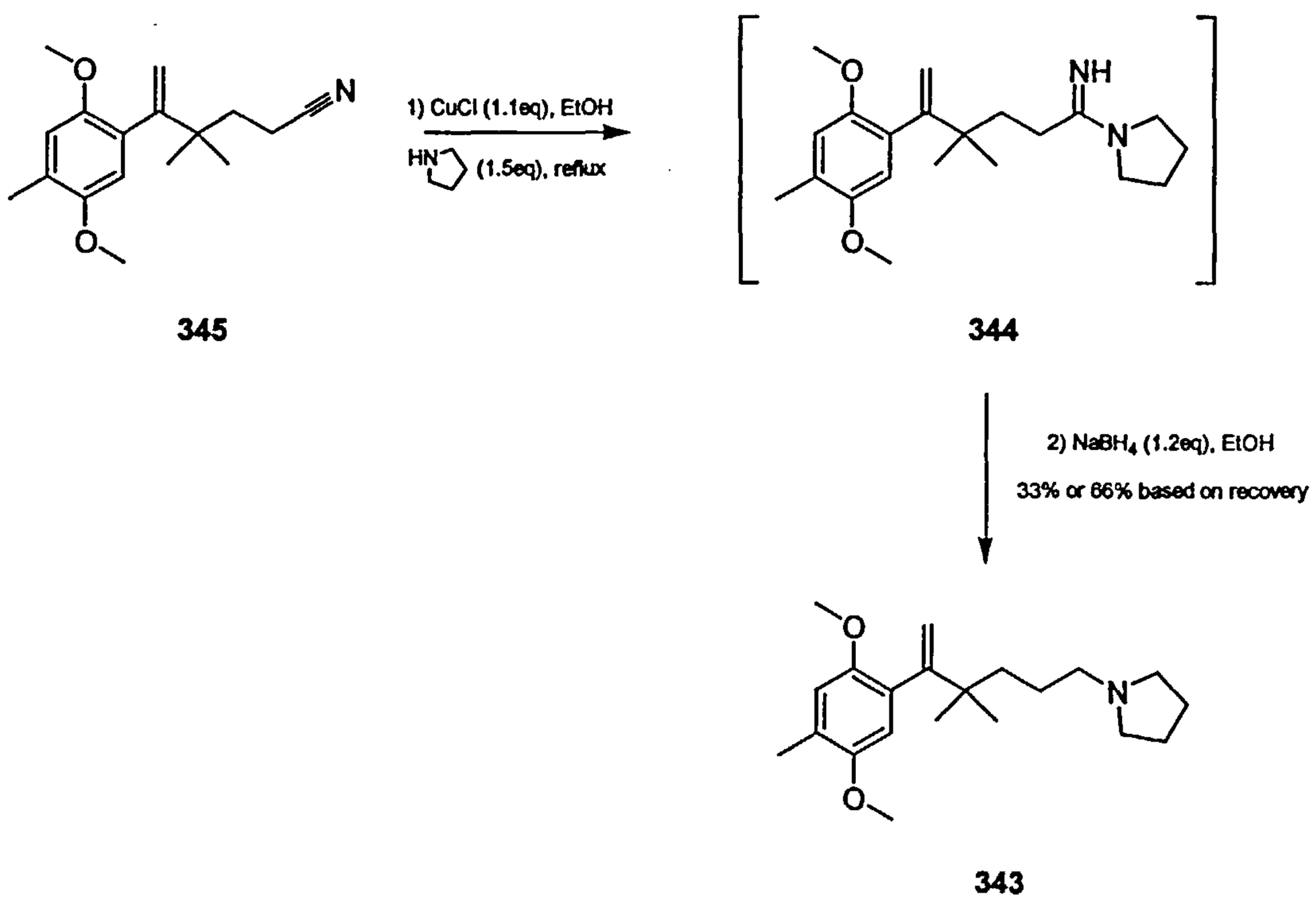


346 345

Scheme 110

Synthesis of 1-[5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-hex-5-enyl]-pyrrolidine (343).

Conversion of nitrile **345** to the styrylamine **343** was accomplished using a modified Capdeviella procedure and was similar to that employed in scheme 95. Copper (I) chloride was added to the nitrile in ethanol followed by the addition of pyrrolidine. After removal of the copper salts, the crude amidine **344** was reduced using $NaBH_4$ to form the desired aminobutyl styene **343**. The yield of the reaction was lower than expected (Scheme 95) and might be due to chelation of the copper with the methoxy groups on the aromatic ring. At this late stage, no attempts to optimise the conditions by increasing the copper loading were considered. The product aminobutyl styrene **343** was isolated by column chromatography and gave spectroscopic data, which correlated well with expectations (Scheme 111).

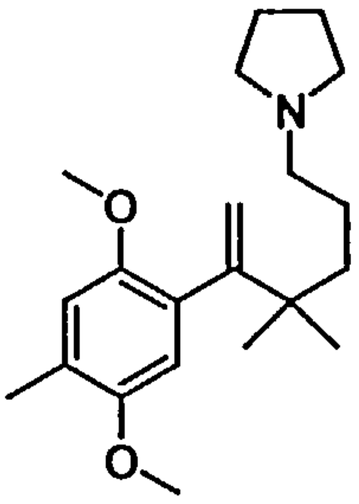


345 **344** **343**

Scheme 111

With the photochemical precursor at hand, attempts were made to construct the ring system *via* the photomediated cyclisation, under similar conditions to that employed earlier. Unfortunately, all attempts to realise this plan met with failure, leading in all cases to mainly decomposition and polymerised products. Currently the reason for this is not clear and work is still in progress to understand these results. Results from the irradiation of aminobutyl styrene **343** under a variety of reaction conditions are shown in the table 5 below.

Table 5: Photo-irradiation results on aminobutyl styrene **343.**

compound	solvent	λ_{max} (nm)	time	product yield (%)
	hexane	medium pressure	20mins	decomposition
	THF	medium pressure	20mins	polymerisation
	MeCN	medium pressure	15mins	decomposition
	benzene	medium pressure	20mins	decomposition
	THF (pyrex filter)	medium pressure	3hours	decomposition

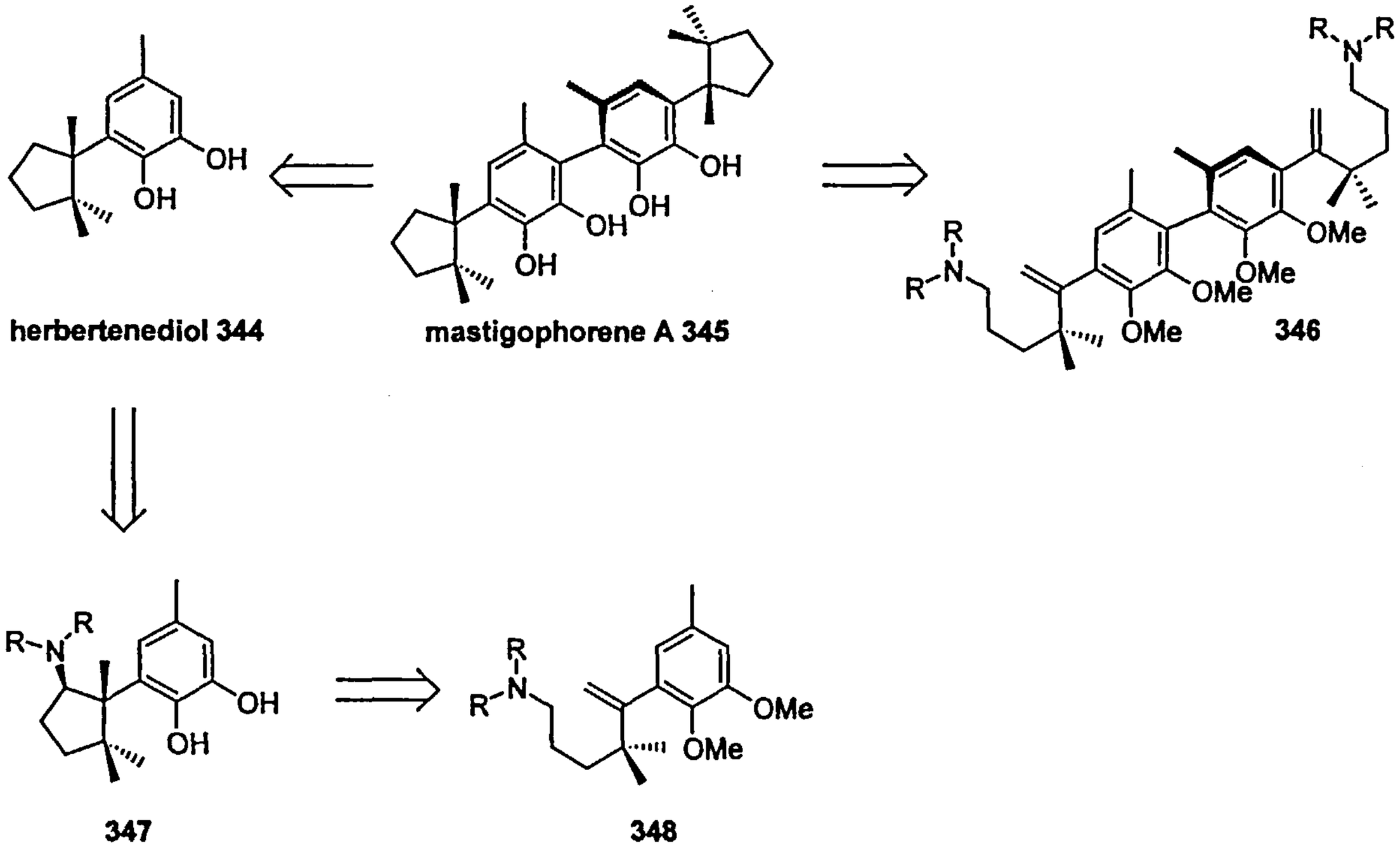
2.9 Conclusion

The work described herein describes a successful synthesis of racemic and enantiomerically pure cuparene *via* the photoelectron transfer initiated cyclisation of highly substituted α-(aminobutyl)styrenes **239** and **286** respectively. The 2:1 ratio of diastereomers **299** and **300** obtained upon irradiation of **286** establishes for the first time that a chiral amine can control (albeit with modest levels of selectivity) the absolute configuration at a hindered quaternary stereocentre formed in this cyclisation.

Furthermore, elaboration of the double bond in **283** has offered a synthesis towards other members of the cuparene class of sesquiterpenes. For example, the synthesis of (±)-cuparenone has also been accomplished as a mixture of α- and γ-isomers via allylic oxidation and double bond reduction.

Future work will concentrate on pursuing other chiral auxiliaries, which both increase the level of selectivity in the photochemical cyclisation and limit the competing Cope elimination during removal of the auxiliary. Although, the attempted photochemical cyclisation towards the enokipodin series of sesquiterpenoids proved unsuccessful, the current approach does seem to be a viable one. One possible approach would be to look at different substituents on the aromatic ring such as halogens or mono-methoxy analogues that can not only tolerate the photochemical cyclisation but can also be converted to the quinone system at a later stage.

A synthesis of mastigophorene A and B could also be considered. Cyclisation of photochemical precursor **348** which could be synthesised by the second-generation approach should provide **347**. The synthesis of herbertenediol by removal of the amine moiety by the methodology discussed followed by deprotection and hydrogenation would constitute a formal total synthesis of mastigophorenes. Alternatively a bi-directional synthesis from bis-amine **346** could be considered, which could be used in a double photomediated ring closure. It would be interesting to see if the axial chirality present in **346** can control the stereochemistry of the two new benzylic quaternary centers. The use of a chiral amine would allow for the investigation of double stereoinduction in the ring closure (Scheme 112).



herbertenediol 344 **mastigophorene A 345** **346**

347 **348**

Scheme 112

Chapter 3

Experimental

General experimental

Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform I.R. spectrometer.

NMR spectra were recorded using a Bruker AM360 or AM400 spectrometer in deuterochloroform, unless otherwise stated, referenced to TMS (δ 0). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (J Hz). The following abbreviations are used: s-singlet, d-doublet, dd-double doublet, t-triplet, q-quartet, m-multiplet.

Mass spectra were recorded on a Jeol AX505W spectrometer (EI) and Kratos MS890 (FAB).

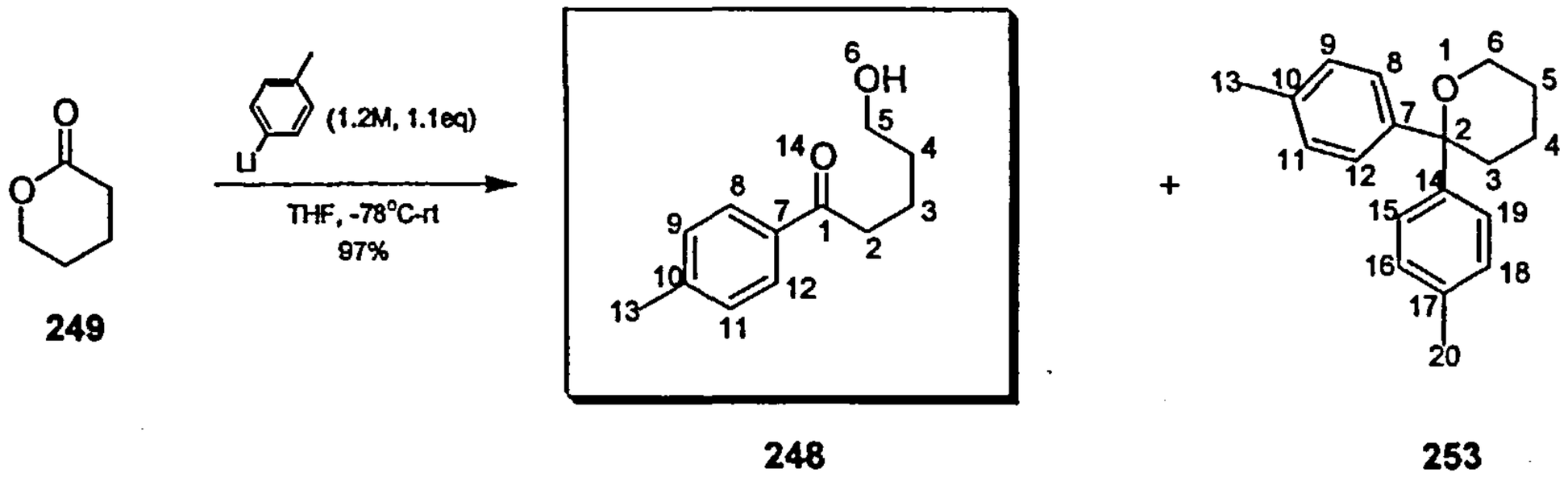
Products were isolated by flash chromatography using Merck silica gel 60 (4063 μm).[152] Analytical t.l.c was carried out on Merck (aluminium sheets) silica gel 60 F_{254} plates using short wave (254 nm) UV light, $KMnO_4$ or anisaldehyde to visualise components.

Irradiations were carried out under an argon atmosphere using an immersion well reactor (model RQ125 and RQ400, Photochemical Reactors Limited) and monitored by t.l.c.

Microwave experiments were carried out using sealed tubes in a CEM Discover microwave reactor.

Dichloromethane was freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Pyrrolidine was distilled from calcium hydride and stored over pellets of potassium hydroxide. *m*-CPBA was purified by dissolving in diethyl ether and then washing three times with a phosphate buffer solution. The solvent was carefully removed *in-vacuo* to give pure *m*-CPBA. All other reagents were used as received.

5-Hydroxy-1-*p*-tolyl-pentan-1-one (248).



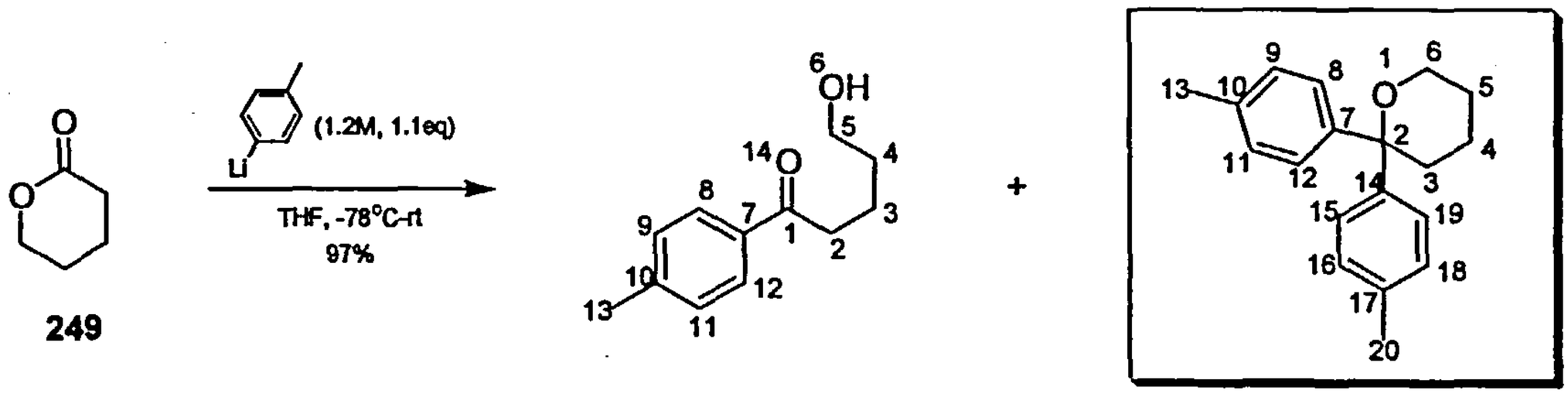
249 248 253

Scheme 52

To a solution of δ-valerolactone (5.02g, 50.14 mmol) in dry THF (40 mL) at -78°C was added *p*-tolyllithium in diethyl ether (46 mL, 1.2M) dropwise over a period of 1 hour. Once the addition was complete, the reaction mixture was left to stir from -78°C to room temperature overnight for 14 hours. The reaction mixture was then cooled back down to -78°C and quenched with water (3 mL), the cooling bath was removed and the reaction mixture was allowed to warm to room temperature with stirring. An additional 20 mL of water was then added, the organic phase was separated and the aqueous phase was extracted with diethyl ether (25 mL x 3). The combined organic phases were dried over magnesium sulphate and the solvent removed by rotary evaporation to afford a yellow oil. Purification by flash column chromatography (diethyl ether/ hexane 1:4) gave compound **248** as a pale yellow oil (9.3 g, 97%); Analytical data agree with that reported in the literature[119]; R_f 0.1 (diethyl ether/ hexane 1:1); δ_H (360 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.2, 7, 12-H), 7.27 (2H, d, *J* 8.2, 9, 11-H), 3.65 (2H, t, *J* 6.1, 5-H), 2.98 (2H, t, *J* 6.4, 2-H), 2.40 (3H, s, 13-H), 1.87-1.57 (5H, m, 3, 4, 6-H); δ_C (90 MHz, $CDCl_3$) 200.2 (1-C), 143.9 (7-C), 134.5 (10-C), 129.3 (8, 12-C), 128.2 (9, 11-C), 62.4

(5-C), 38.0 (2-C), 32.3 (4-C), 21.7 (13-C), 20.3 (3-C); *m/z* (EI) 193 ($[M+H]^+$; 7), 192 (M^+; 29), 174 (71), 147 (33), 119 (100), 91 (83), 84 (48), 65 (69).

2, 2-Di-*p*-tolyl-tetrahydropyran (253).

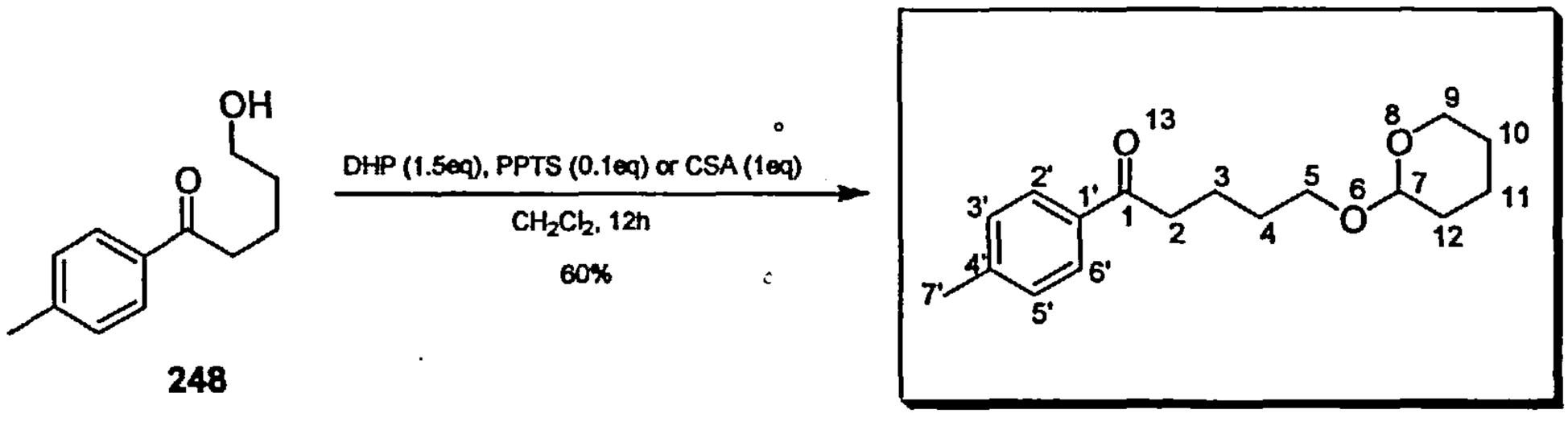


Scheme 52

To a solution of δ-valerolactone (4.35 g, 45.83 mmol) in dry THF (40 mL) at -78˚C was added *p*-tolyllithium in diethyl ether (60 mL, 1.2M) dropwise over a period of 1 hour. Once the addition was complete, the reaction mixture was left to stir from -78˚C to room temperature overnight for 14 hours. The reaction mixture was then cooled back down to -78˚C and quenched with water (3 mL), the cooling bath was removed and the reaction mixture was allowed to warm to room temperature with stirring. An additional 20 mL of water was then added, the organic phase was separated and the aqueous phase was extracted with diethyl ether (25 mL x 3). The combined organic phases were dried over magnesium sulphate and the solvent removed by rotary evaporation to afford a yellow oil. Purification by flash column chromatography (diethyl ether/ hexane 1:4) gave compound **248** as a pale yellow oil (3.05 g, 25%); R_f 0.7 (diethyl ether/ hexane 1:1); δ_H (360 MHz, $CDCl_3$) 7.27 (4H, d, *J* 8.2, 8, 12, 15, 19-H), 7.11 (4H, d, *J* 8.1, 9, 11, 16, 18-H), 3.7 (2H, t, *J* 5.3, 6-H), 2.29 (6H, s, 13, 20-H), 2.29-2.24 (2H, m, 3-H), 1.72-

1.57 (4H, m, 4, 5-H); δ_C (90 MHz, $CDCl_3$) 143.8 (7, 14-C), 136.4 (10, 17-C), 129.4 (9, 11, 16, 18-C), 126.7 (8, 12, 15, 19-C), 80.0 (2-C), 63.3 (6-C), 36.1 (3-C), 26.4 (5-C), 21.4 (13, 20-C), 21.1 (4-C); *m/z* (EI) 267 ($[M+H]^+$; 22), 266 (M^+; 87), 251 (36), 223 (9), 210 (13), 195 (31), 182 (21), 175 (100), 165 (9), 119 (80), 105 (9), 91 (29).

5-[(Tetrahydropyranyl)oxy]-1-*p*-tolyl-pentan-1-one (247).



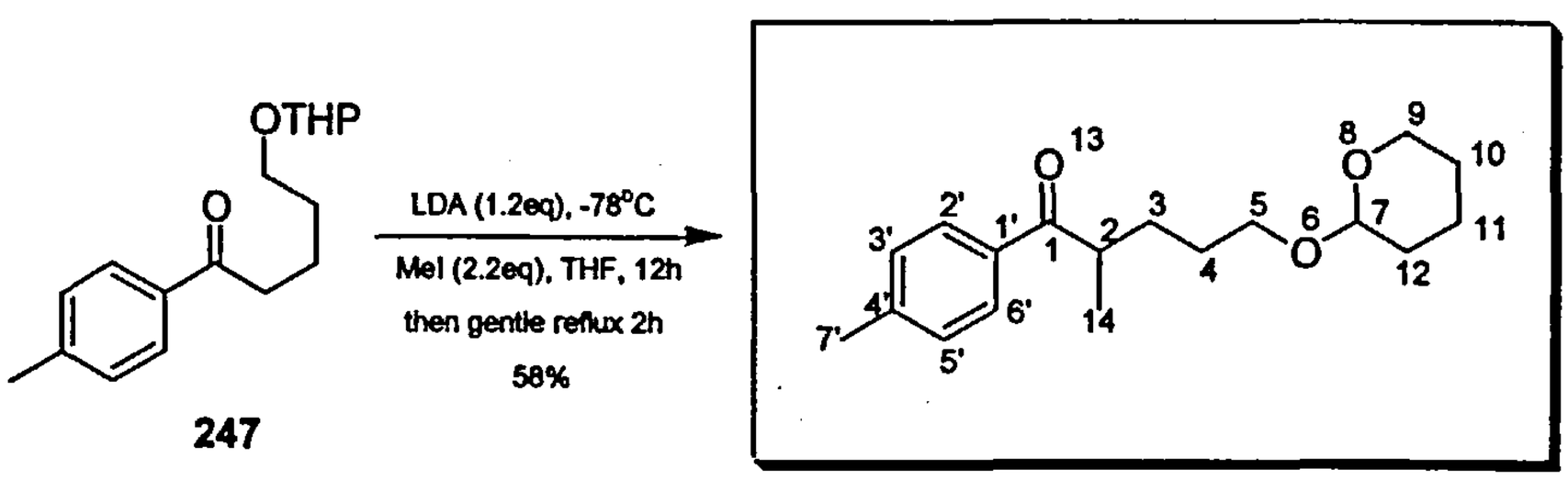
248 **247**

Scheme 54

To a solution of 5-hydroxy-1-p-tolyl-pentan-1-one **248** (4.17 g, 21.7 mmol) in dichloromethane (25 mL) was added under an argon atmosphere 3,4-dihydro-2H-pyran (3.65 mL, 32.6 mmol) and pyridinium *p*-toluenesulfonate (0.57 g, 2.17 mmol) in dichloromethane (100 mL). The reaction mixture was left to stir at room temperature for 12 hours and indicated by TLC to be complete. The mixture was then diluted with diethyl ether (100 mL) and washed with half-saturated brine (50 mL x 2). The organic layer was then dried over magnesium sulphate and rotary evaporated to yield a yellow liquid. The crude product was purified by flash column chromatography (diethyl ether/hexane 1:4) to afford the pure THP-ether **247** as a pale yellow oil (3.6 g, 60%); Analytical data agree with that reported in the literature[119]; R_f 0.36 (diethyl ether/hexane

1:4); δ_H (360 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.1, 2', 6'-H), 7.26 (2H, d, *J* 8.1, 3', 5'-H), 4.58 (1H, t, *J* 3.5, 7-H), 3.89-3.76 (2H, m, 9-H), 3.51-3.41 (2H, m, 10-H), 2.99 (2H, t, *J* 7.3, 5-H), 2.40 (3H, s, 7'-H), 1.87-1.49 (10H, m, 2, 3, 4, 11, 12-H); δ_C (90 MHz, $CDCl_3$) 200.4 (1-C), 144.1 (4'-C), 135.0 (1'-C), 129.7 (3', 5'-C), 128.6 (2', 6'-C), 99.3 (7-C), 67.7 (9-C), 62.8 (5-C), 38.6 (2-C), 31.2 (12-C), 29.8 (4-C), 25.9 (10-C), 22.1 (7'-C), 21.7 (3-C), 20.1 (11-C); *m/z* (EI) 276 (M^+; 2), 191 (82), 175 (93), 147 (71), 134 (73), 119 (97), 85 (88), 65 (76), 55 (100).

5-[(Tetrahydropyranyl)oxy]-2-methyl-1-*p*-tolyl-pentan-1-one (246).

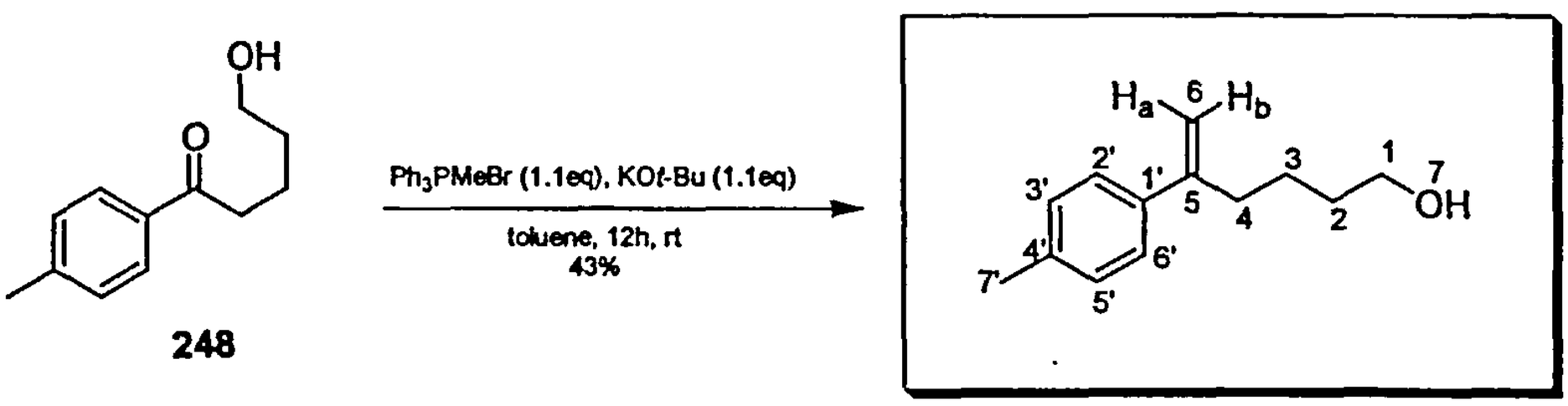


Scheme 55

To an oven dry 50 mL three neck round bottom flask, equipped with a condenser, pressure equalising funnel and an argon inlet was added dry diisopropylamine (1.78 mL, 12.7 mmol) and THF (5 mL). The mixture was then cooled to -78°C and n-butyllithium (6.12 mL, 2.07M, 12.7 mmol) in hexanes was then added dropwise. The resulting pale yellow solution was stirred for 30 minutes at -78°C and then brought to 0°C, where it was further stirred for 20 minutes to ensure complete formation of LDA. The solution was then cooled back down to -78°C and 5-[(tetrahydropyranyl)oxy]-1-*p*-

tolyl-pentan-1-one **247** in THF (10 mL) was added dropwise via the pressure equalising funnel over a period of 30 minutes. The mixture was then left to stir for 45 minutes at –78°C. A solution of iodomethane (1.47 mL, 23.2 mmol) in THF (3 mL) was then added, the cooling bath was removed and the reaction left to stir overnight at room temperature for 18 hours and then gently refluxed for 2 hours. After cooling to room temperature the reaction was poured into saturated ammonium chloride (20 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (25 mL x 2). The combined organics were dried over magnesium sulphate and concentrated. The residue was diluted with diethyl ether (25 mL) and washed successively with hydrochloric acid (1M, 10 mL), 10% sodium thiosulphate and brine. After drying over magnesium sulphate the organics were concentrated and purified by flash column chromatography (diethyl ether/hexane 1:4) to afford **246** (1.76 g, 58%) as a colourless oil; Analytical data agree with that reported in the literature[119]; R_f 0.44 (diethyl ether/hexane 1:1); ν_{max} (neat)/cm^{-1} 1680 (s, C=O), 1607 (s), 1454 (m), 1376 (m), 1353 (m), 1034 (s), 972 (s); δ_H (360 MHz, $CDCl_3$) 7.88-7.86 (2H, m, 2', 6'-H), 7.26 (2H, d, *J* 8.0, 3', 5'-H), 4.56-4.53 (1H, m, 7-H), 3.86-3.81 (1H, m, 2-H), 3.76-3.70 (1H, m, 9-H), 3.53-3.40 (2H, m, 5-H), 3.41-3.34 (1H, m, 9-H), 2.41 (3H, s, 7'-H), 1.91-1.43 (10H, m, 3, 4, 10, 11, 12-H), 1.21 (3H, d, *J* 6.9, 14-H); δ_C (90 MHz, $CDCl_3$) 204.4 (1-C), 144.0 (4'-C), 134.6 (1'-C), 129.7 (3', 5'-C), 128.9 (2', 6'-C), 99.3 (7-C), 67.8 (9-C), 62.8 (5-C), 40.6 (2-C), 31.2 (12-C), 30.8 (4-C), 27.9 (10-C), 25.9 (3-C), 22.0 (7'-C), 20.1 (11-C), 17.8 (14-C); m/z (EI) 291 ($[M+H]^+$; 1), 290 (M^+; 5), 205 (67), 189 (85), 148 (46), 119 (100), 99 (48), 85 (83), 65 (64), 55 (82).

5-*p*-Tolyl-5-hexen-1-ol (256).



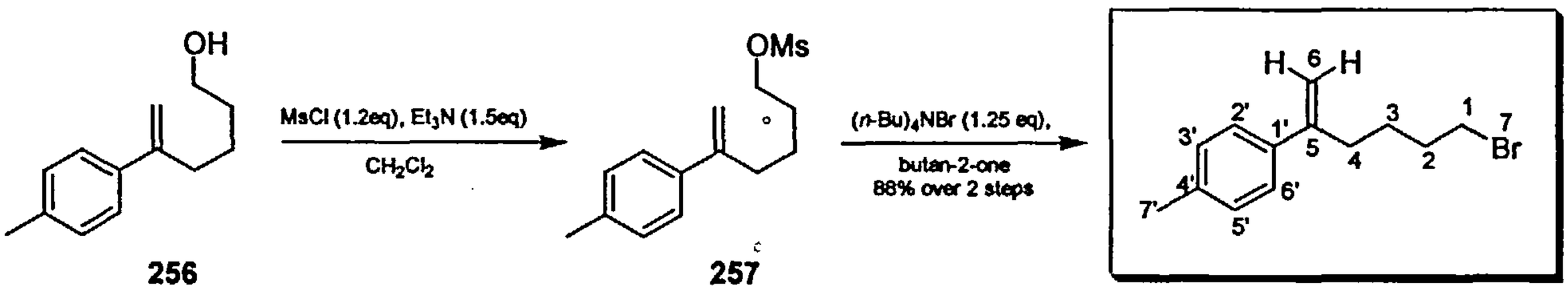
256

Scheme 57

A suspension of methyltriphenylphosphonium bromide (7.16 g, 20.1 mmol) and potassium *tert*-butoxide (2.25 g, 20.1 mmol) in toluene (50 mL) was cooled to 0°C in a three neck round bottom flask, equipped with a magnetic stirrer, condenser, pressure equalising funnel and argon inlet. The bright yellow suspension was stirred at 0°C for 15 minutes and then refluxed for 1 hour. The ylide mixture was re-cooled to 0°C and a solution of 5-hydroxy-1-phenyl-1-pentanone **248** (3.5 g, 18.2 mmol) in toluene (10 mL) was added dropwise via the pressure equalising funnel. The resulting mixture was stirred at 0°C for 10 minutes and at ambient temperature overnight. The reaction mixture was poured into aqueous hydrochloric acid (10%, 20ml) and extracted with diethyl ether (40 mL x 2). The combined organic extracts were washed with water (20 mL), dried over magnesium sulphate and concentrated to afford a yellow oil that was purified by flash column chromatography (petroleum ether/diethyl ether 1:1) to give **256** as a colourless oil (1.47 g, 43%); Analytical data agree with that reported in the literature[119]; R_f 0.22 (petroleum ether/diethyl ether 1:1); ν_{max} (neat)/cm^{-1} 3338 (bs, OH), 2937 (s), 1624 (m), 1513 (s), 1457 (m), 1057 (m), 891 (s), 824 (s); δ_H (360 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.1, 2', 6'-H), 7.13 (2H, d, *J* 7.9, 3', 5'-H), 5.24 (1H, d, *J* 1.3, 6-

H_a), 5.01 (1H, d, *J* 1.2, 6-H_b), 3.61 (2H, t, *J* 6.4, 1-H), 2.51 (2H, t, *J* 7.1, 4-H), 2.33 (3H, s, 7'-H), 1.61-1.49 (4H, m, 2, 3-H), 1.34 (1H, bs, 7-H); δ_C (90 MHz, $CDCl_3$) 148.1 (5-C), 138.3 (4'-C), 137.1 (1'-C), 129.0 (3', 5'-C), 126.0 (2', 6'-C), 111.7 (6-C), 62.9 (1-C), 35.1 (4-C), 32.4 (2-C), 24.4 (3-C), 21.1 (7'-C); *m/z* (EI) 191 ($[M+H]^+$; 8), 190 (M^+; 57), 157 (23), 145 (30), 132 (92), 119 (100), 105 (37), 91 (60), 77 (14).

6-Bromo-2-p-tolyl-hex-1-ene (255).



256 **257** **255**

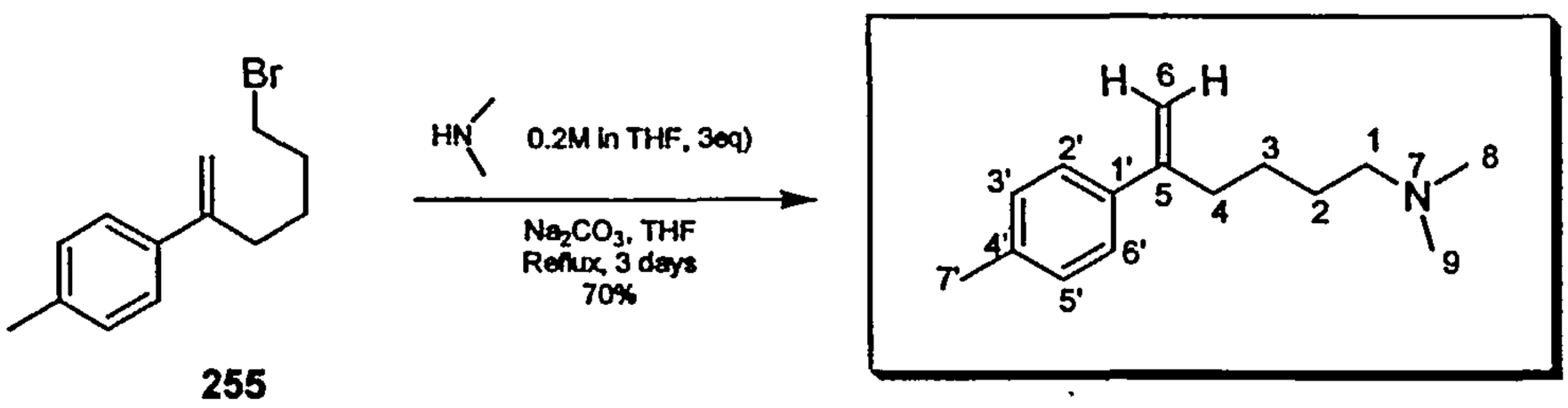
Scheme 58

To a cold (-10°C) magnetically stirred solution of 5-p-tolyl-5-hexen-1-ol **256** (0.69 g, 3.6 mmol) and triethylamine (0.75 mL, 5.4 mmol) in dichloromethane (18 mL) was added methanesulfonyl chloride (0.33 mL, 4.3 mmol) dropwise over 5 minutes and the reaction left to stir at room temperature for 16 hours (under an argon atmosphere). The resulting orange/brown solution was then poured into aqueous HCl (25ml, 1M) and extracted with dichloromethane (20 mL x 3). The dichloromethane extract was washed with saturated sodium hydrogen carbonate and brine. The organic layer was dried over magnesium sulphate and rotary evaporated to afford the crude mesylate **257** (0.9 g, 93%) as a yellow oil which was used without further purification.

To a solution of mesylate **257** (0.9 g, 3.4 mmol) in butan-2-one (3 mL) was added tetra-n-butyl ammonium bromide (1.35 g, 4.2 mmol), carried out in a 25 mL two neck round

bottom flask equipped with an argon inlet and magnetic stirrer. The resulting orange/brown homogenous mixture was left to stir for 16 hours at room temperature. Once reaction was complete by tlc the butan-2-one was removed under reduced pressure and the residue was taken up in DCM (20 mL). The organic phase was washed with $NaHCO_3$ (x2), brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an orange oil which was purified by flash column chromatography (hexane) to furnish alkyl bromide **255** as a colourless oil (0.8 g, 88% over 2 steps); Analytical data agree with that reported in the literature[119]; R_f 0.48 (hexane); δ_H (360 MHz, $CDCl_3$) 7.30 (2H, d, J 8.1, 2', 6'-H), 7.14 (2H, d, J 8.2, 3', 5'-H), 5.25 (1H, d, J 1.3, 1-H_a), 5.02 (1H, dd, J 2.3 and 1.3, 1-H_b), 3.38 (2H, t, J 6.8, 6-H), 2.53-2.49 (2H, m, 3-H), 2.34 (3H, s, 7'-H), 1.91-1.84 (2H, m, 5-H), 1.62-1.53 (2H, m, 4-H); δ_C (90 MHz, $CDCl_3$) 148.1 (2-C), 138.4 (4'-C), 137.6 (1'-C), 129.5 (3', 5'-C), 126.4 (2', 6'-C), 112.4 (1-C), 34.8 (6-C), 34.1 (3-C), 32.8 (5-C), 27.1 (4-C), 21.5 (7'-C)

Dimethyl-(5-*p*-tolyl-hex-5-enyl)amine (257).



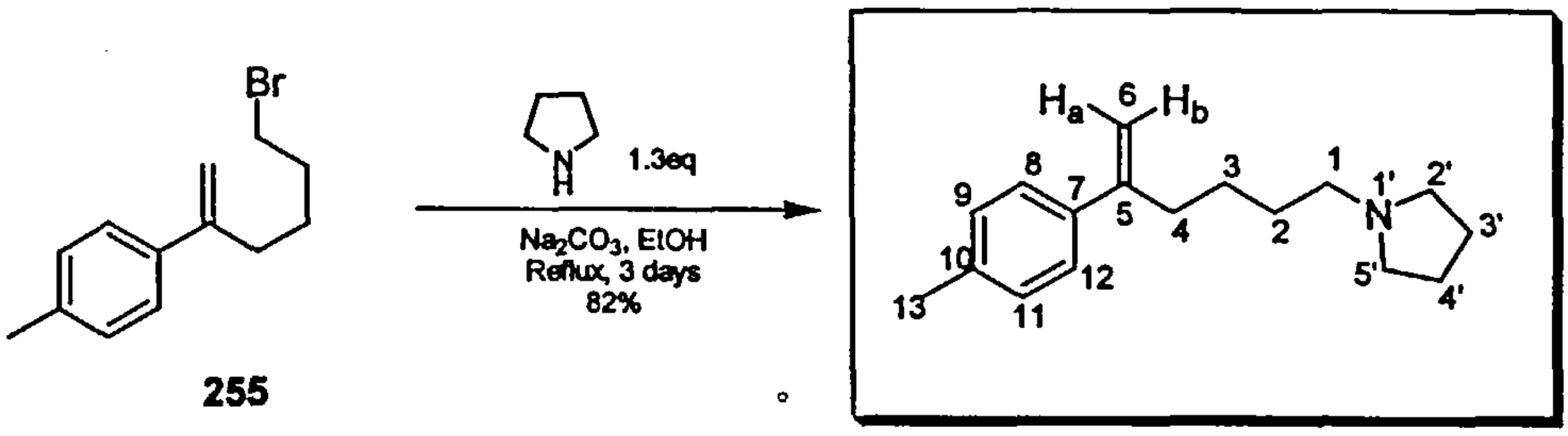
255 **257**

Scheme 59

In an oven dried 50 mL two neck round bottom flask equipped with a condenser and under an argon atmosphere was added 6-bromo-2-p-tolyl-hex-1-ene **255** (0.52 g, 1.85 mmol) and a solution of dimethylamine in THF (0.2 M, 27.8 mL, 5.6 mmol). To this mixture was then added Na_2CO_3 (1.96 g, 18.5 mmol) and the suspension refluxed for three days. The resulting pale yellow suspension was then cooled down to room temperature and diluted with ethyl acetate (50 mL). The mixture was then filtered and the solid was washed thoroughly with ethyl acetate (25 mL x 3). The filtrate was then concentrated by rotary evaporation to yield a yellow oil, which was purified by flash column chromatography (diethyl ether: petroleum: triethylamine 1:3:0.1) to furnish 257 as a colourless oil (0.28 g, 70%); R_f 0.14 (diethyl ether/petroleum ether/triethylamine 1:1:0.1); ν_{max} (neat)/cm^{-1} 2937 (s), 2857 (s), 2761 (s), 1899 (w), 1786 (w), 1624 (m), 1513 (w), 1459 (s), 1040 (m), 823 (s); δ_H (360 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.1, 2', 6'-H), 7.13 (2H, d, *J* 8.0, 3', 5'-H), 5.23 (1H, d, *J* 1.4, 6-H_a), 5.01 (1H, d, *J* 1.3, 6-H_b), 2.50 (2H, t, *J* 6.6, 1-H), 2.34 (3H, s, 7'-H), 2.23 (2H, t, *J* 7.18, 4-H), 2.19 (6H, s, 8, 9-H), 1.49-1.46 (4H, m, 2, 3-H); δ_C (90 MHz, $CDCl_3$) 148.2 (5-C), 138.4 (4'-C), 136.9 (1'-C), 128.9 (3', 5'-C), 125.9 (2', 6'-C), 111.5 (6-C), 59.7 (1-C), 45.5 (8, 9-C), 35.3 (2-C), 27.4 (2-C), 26.1 (3-C), 21.1 (7'-C); m/z (EI) 218 ($[M+H]^+$; 20), 217 (M^+; 100), 174

(12), 157 (10), 129 (5), 98 (5), 84 (40), 58 (14); HRMS m/z (EI) calculated for $C_{15}H_{23}N$, 217.18304 (M^+), found 217.1836.

1-(5-*p*-Tolyl-hex-5-enyl)pyrrolidine (254).



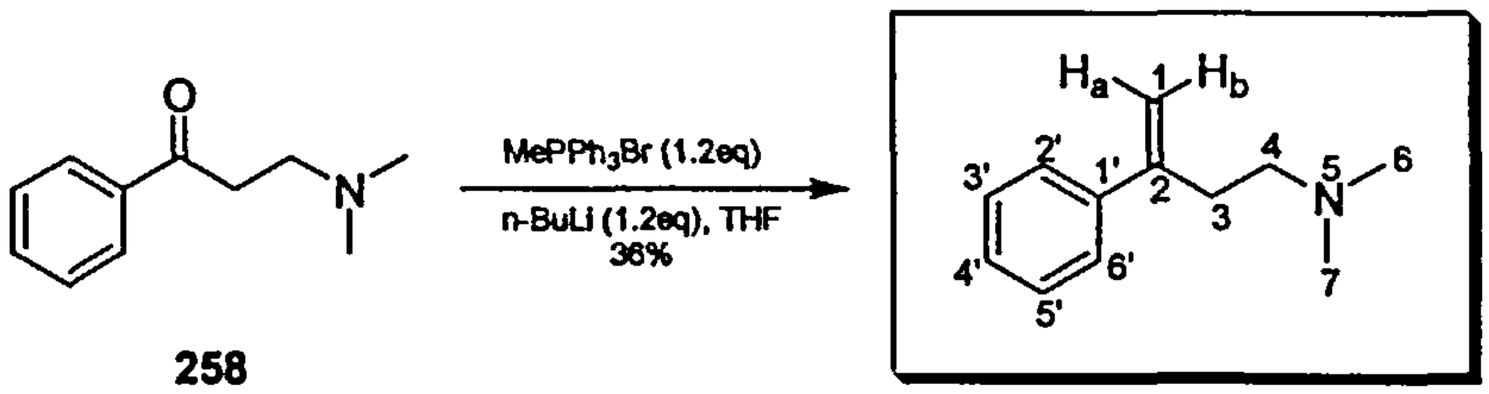
255 **254**

Scheme 59

To a solution of 6-bromo-2-p-tolyl-hex-1-ene **255** (101 mg, 0.36 mmol) in absolute ethanol (5 mL) was sequentially added pyrrolidine (36 μL, 0.43 mmol) and anhydrous sodium carbonate (0.38 g, 3.6 mmol). The resulting suspension was refluxed for 2 days. The mixture was then diluted with ethyl acetate, filtered and concentrated in vacuo to give a yellow oil. The crude product was purified by flash column chromatography (diethyl ether: petroleum ether: triethylamine 1:3:0.1) to yield **254** as a pale yellow oil (72 mg, 82%); R_f 0.19 (diethyl ether/petroleum ether 1:1); δ_H (360 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.1, 8, 12-H), 7.05 (2H, d, *J* 8.2, 9, 11-H), 5.16 (1H, d, *J* 1.3, 6-H_a), 4.93 (1H, d, *J* 1.2, 6-H_b), 2.45-2.31 (8H, m, 2', 5', 1, 4-H), 2.27 (3H, s, 13-H), 1.72-1.65 (4H, m, 3', 4'-H), 1.49-1.37 (4H, m, 2, 3-H); δ_C (90 MHz, $CDCl_3$) 149.2 (5-C), 139.4 (10-C), 138.0 (7-C), 129.9 (9, 11-C), 127.0 (8, 12-C), 112.5 (6-C), 57.5 (1-C), 55.3 (2', 5'-C),

36.3 (4-C), 29.7 (2-C), 27.3 (3-C), 24.4 (3', 4'-C), 22.1 (13-C); m/z (EI) 244 ($[M+H]^+$; 4), 243 (M^+; 21), 124 (5), 110 (30), 96 (7), 84 (100), 55 (7), 44 (7).

4-(Dimethylamino)-2-phenyl-1-butene (259).



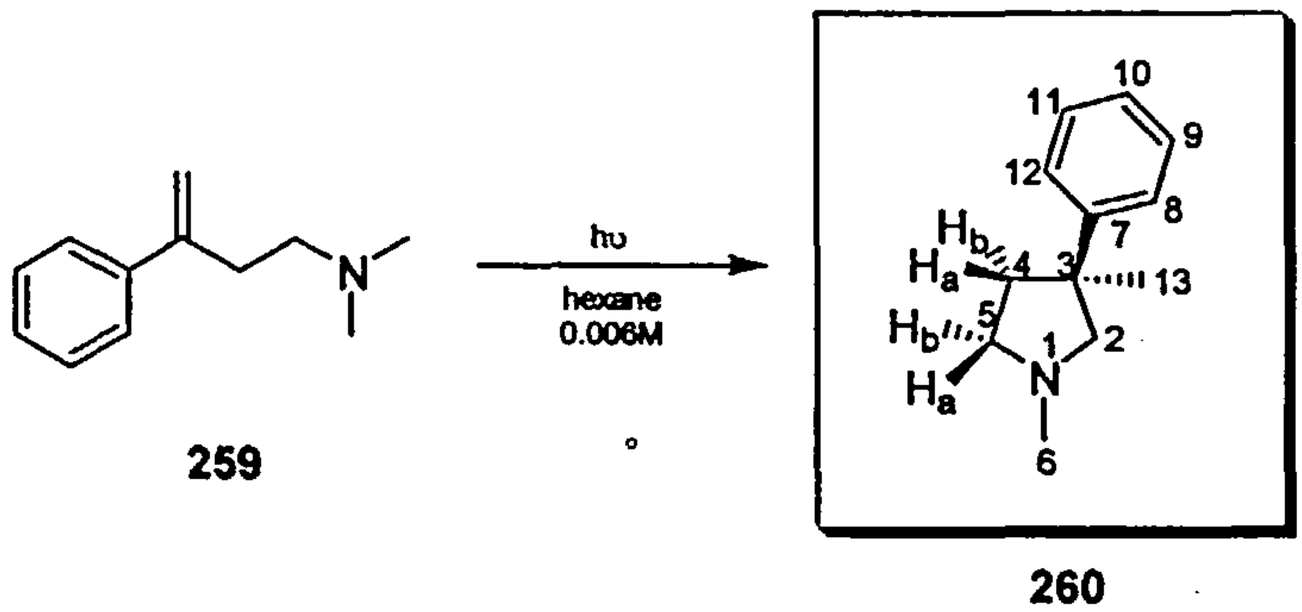
258 **259**

Scheme 60

To methyltriphenylphosphonium bromide (1.99 g, 5.56 mmol) in THF (50 mL) was added butyllithium (1.98M in hexanes, 2.8 mL, 5.56 mmol) dropwise at -78°C. The resulting bright yellow mixture was stirred at room temperature for 1 hour and then cooled to 0°C. To the cold phosphorous ylide was then added 3-dimethylamino-1-phenyl-propan-1-one **258** (0.99 g, 4.6 mmol) dissolved in THF (10 mL) and the reaction left to stir at room temperature for 12 hours. Methanol (5 mL) and water was then added and the aqueous layer was extracted with benzene (20 mL x 3). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous magnesium sulphate and rotary evaporated to give a brown viscous oil. The styryl amine **259** was purified by flash column chromatography (diethyl ether/ petroleum ether/ triethylamine 1:4:0.1) to afford a pale yellow oil (354 mg, 36%); Analytical data agree with that reported in the literature[126]; R_f 0.33 (diethyl ether/ petroleum ether/ triethylamine 1:1:0.1); δ_H (360 MHz, $CDCl_3$) 7.43-7.41 (2H, m, 2', 6'-H), 7.34-7.26

(3H, m, 3', 4', 5'-H), 5.31 (1H, d, *J* 1.2, 1-H_a), 5.10 (1H, d, *J* 1.2, 1-H_b), 2.69 (2H, t, *J* 7.9, 4-H), 2.40 (2H, t, *J* 7.9, 3-H), 2.25 (6H, s, 6, 7-H).

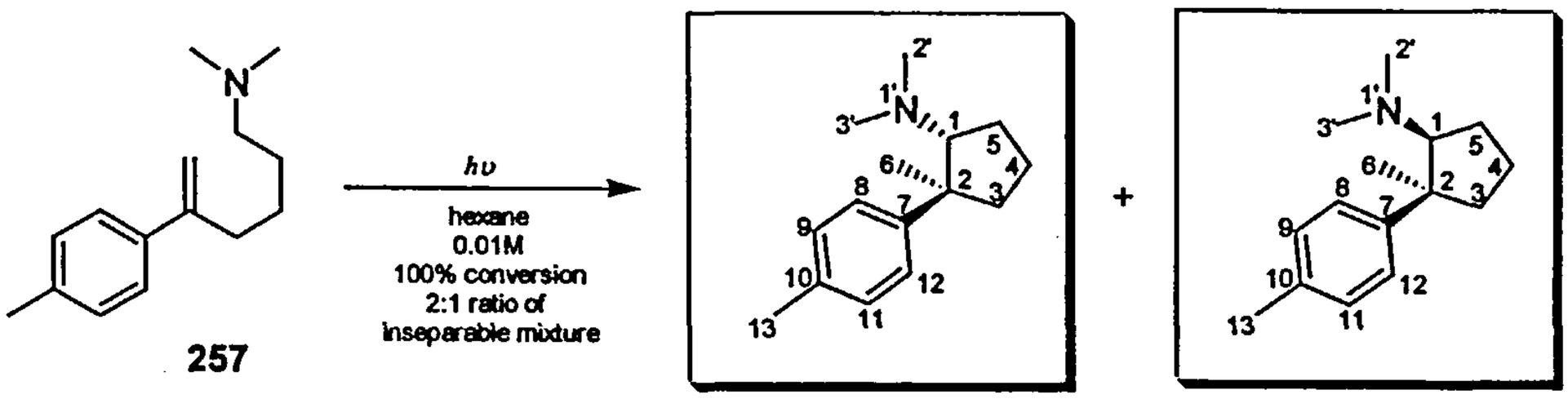
1, 3-Dimethyl-3-phenylpyrrolidine (260).



Scheme 61

A hexane solution of styryl amine **259** (0.006M, 354 mg, 1.7 mmol) was placed in a quartz vessel and purged with argon for 1 hour. The solution was then irradiated for 5 hours using a medium pressure 400W mercury lamp. After removal of the solvent, crude NMR of the irradiated sample gave all the characteristic peaks for product **260** and required no further purification; Analytical data agree with that reported in the literature[126]; R_f 0.1 (diethyl ether/ hexane 1:1); δ_H (360 MHz, $CDCl_3$) 7.34-7.16 (5H, m, 8, 9, 10, 11, 12-H), 2.94-2.88 (1H, m, 5-H_a or H_b), 2.78 (2H, d, J 1.8, 2-H), 2.59-2.53 (1H, m, 5-H_a or H_b), 2.40 (3H, s, 6-H), 2.27-2.21 (1H, m, 4-H_a or H_b), 2.01-1.95 (1H, m, 4H_a or H_b), 1.45 (3H, s, 13-H).

(1RS, 2SR)-Dimethyl-(2-methyl-2-p-tolyl-cyclopentyl)-amine (261a) and (1SR, 2SR)-Dimethyl-(2-methyl-2-p-tolyl-cyclopentyl)-amine (261b).



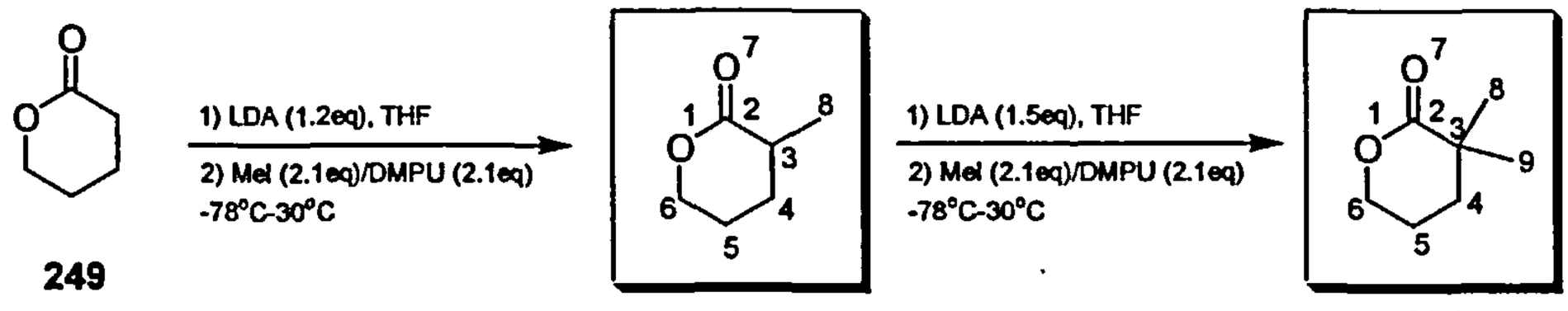
Scheme 62

A hexane solution (280 mL, 0.01M) of styryl amine dimethyl-(5-*p*-tolyl-hex-5-enyl)-amine **257** (0.7 g, 3.23 mmol) was placed in a quartz vessel and purged with argon for 1 hour. The solution was then irradiated with a medium pressure 400W mercury lamp for 6 hours. NMR analysis of the irradiated sample showed 100% conversion and the formation of two products in a 2:1 ratio, which were tentatively assigned as **261a** and **261b**. The products were inseparable by column chromatography and were assigned from data obtained from the isomer mixture.

Data for **261a** (major): R_f 0.28 (hexane/trimethylamine 19:1); δ_H (360 MHz, $CDCl_3$) 7.33 (2H, d, *J* 8.2, 8, 12-H), 7.09 (2H, d, *J* 8.0, 9, 11-H), 2.76 (1H, t, *J* 8.6, 1-H), 2.31 (3H, s, 13-H), 2.22-2.10 (2H, m, 5-H), 1.97 (6H, s, 2', 3'-H), 1.90-1.70 (4H, m, 3, 4-H), 1.37 (3H, s, 6-H)

Partial ^{1}H-NMR data for **261b** (minor): R_f 0.28 (hexane/trimethylamine 19:1); δ_H (360 MHz, $CDCl_3$) 2.60 (1H, t, *J* 7.4, 1H), 1.95 (6H, s, 2', 3'-H).

3-Methyl-tetrahydro-pyran-2-one (265) and 3, 3-dimethyl-tetrahydro-pyran-2-one (264).



249 **265** **264**

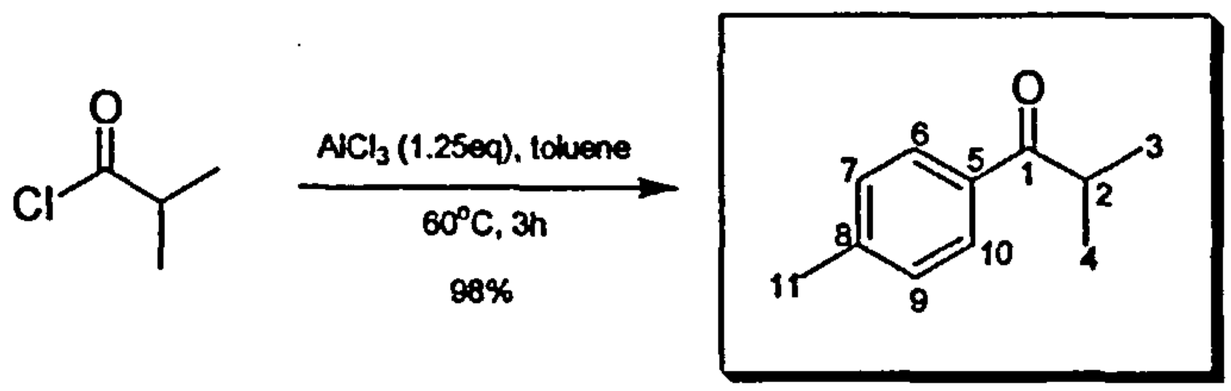
Scheme 64

To a stirred solution of freshly distilled diisopropylamine (8.85 mL, 62.37 mmol) in dry THF (50 mL) was added a solution of *n*-butyllithium in hexane (1.98M, 31.5 mL, 62.37 mmol) at -78˚C under argon. The reaction was stirred at this temperature for 20 minutes after which the ice bath was removed and the temperature raised to 0˚C. The mixture was stirred at this temperature for 30 minutes and the resulting pale yellow solution was cooled back down to -78˚C. To the solution was added as quickly as possible δ-valerolactone **249** (5 g, 49.9 mmol) dissolved in THF (50 mL). After stiring for 1 hour at -78˚C, iodomethane (9.7 mL, 104.8 mmol) in DMPU (12.1 mL, 99.8 mmol) was added. The resulting mixture was stirred at -78˚C for 15 minutes and then at -30˚C for 3 hours. The resulting mixture was then quenched with saturated ammonium chloride and extracted diluted with diethyl ether (100 mL). The organic phase was separated from the aqueous and the aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organics were dried over magnesium sulphate and rotary evaporated under reduced pressure to afford **265** as a yellow oil which was used in the next step without further purification; Analytical data agree with that reported in the literature[128]; δ_H (360 MHz, $CDCl_3$) 4.35-4.29 (2H, m, 6-H), 2.62-2.54 (1H, m, 3-H),

2.15-2.00 (1H, m, 4 or 5-H), 1.92-1.88 (2H, m, 4 or 5-H), 1.58-1.50 (1H, m, 4 or 5-H), 1.27 (3H, s, 8-H).

To a stirred solution of freshly distilled diisopropylamine (10.6 mL, 74.85 mmol) in dry THF (50 mL) was added a solution of *n*-butyllithium in hexane (1.98M, 37.8 mL, 74.85 mmol) at -78°C under argon. The reaction was stirred at this temperature for 20 minutes after which the ice bath was removed and the temperature raised to 0°C. The mixture was stirred at this temperature for 30 minutes and the resulting pale yellow solution was cooled back down to -78°C. To the solution was added as quickly as possible 3-methyl-tetrahydro-pyran-2-one **265** (5 g, 49.9 mmol) dissolved in THF (50 mL). After stiring for 1 hour at -78°C, iodomethane (9.72 mL, 104.8 mmol) in DMPU (12.7 mL, 104.79 mmol) was added. The resulting mixture was stirred at -78°C for 15 minutes and then at -30°C for 5 hours. The resulting mixture was then quenched with saturated ammonium chloride and extracted diluted with diethyl ether (100 mL). The organic phase was separated from the aqueous and the aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organics were dried over magnesium sulphate and rotary evaporated under reduced pressure to afford **264** as a yellow oil (crude yield 90%). The product **264** could be purified by kugelrohr distillation; Analytical data agree with that reported in the literature[128a]; δ_H (360 MHz, $CDCl_3$) 4.35 (2H, t, *J* 5.7, 6-H), 1.94-1.88 (2H, m, 5-H), 1.78-1.75 (2H, m, 4-H), 1.30 (6H, s, 8, 9-H).

2-Methyl-1-*p*-tolyl-propan-1-one (269).

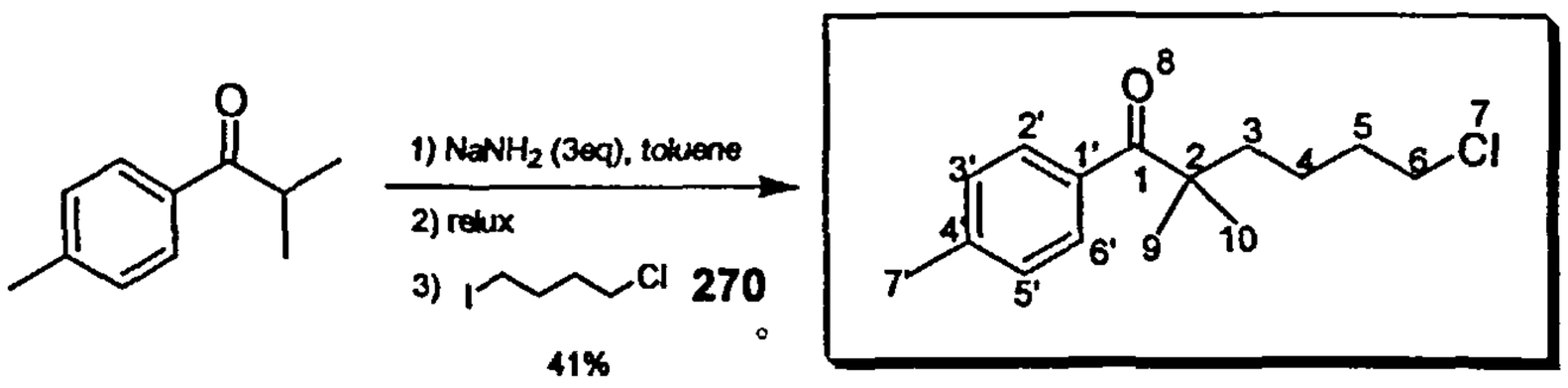


269

To powdered $AlCl_3$ (30.8 g, 224.99 mmol) in a 500 mL, three neck round bottom flask equipped with an argon inlet, magnetic stirrer, double face condenser, pressure equalising dropping funnel and a HCl gas outlet bubbling into water, was added toluene (67 mL, 629.96 mmol). Isobutyryl chloride (18.8 mL, 179.99 mmol) was then added dropwise to the yellow solution over a period of 30 minutes. Once the addition was complete the reaction mixture was heated to 60°C for 3 hours. The resulting dark green/black mixture was then poured into water (400 mL) and ice. The organic phase was separated from the aqueous and the aqueous was extracted with ether (x3). The combined organic layers were washed with NaOH (x2, 10%), water (x1), brine (x1), dried over magnesium sulphate and concentrated under reduced pressure to give the crude product as an orange/brown oil. Fractional distillation through a vigreux column under water pump pressure afforded the title compound **269** as a colourless oil (28.7g, 98%); Analytical data agree with that reported in the literature[130]; ν_{max} (neat)/cm^{-1} 3029 (m), 2972 (m), 2932 (m), 2872 (m), 2360 (m), 1678 (s), 1607 (s), 1223 (s), 1161 (m), 977 (m), 830 (m); δ_H (360 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.0, 6, 10-H), 7.27 (2H, d, *J* 8.0, 7, 9-H), 3.56 (1H, m, 2-H), 2.20 (3H, s, 11-H), 1.21 (6H, d, *J* 6.9, 3, 4-H); δ_C (90 MHz,

$CDCl_3$) 204.1 (1-C), 143.5 (5-C), 133.7 (8-C), 129.3 (6, 10-C), 128.4 (7, 9-C), 35.2 (2-C), 21.6 (11-C), 19.2 (3, 4-C); *m/z* (EI) 162 (M^+; 12), 119 (100), 105 (14.9), 91 (22%).

6-Chloro-2, 2-dimethyl-1-*p*-tolyl-hexan-1-one (271).

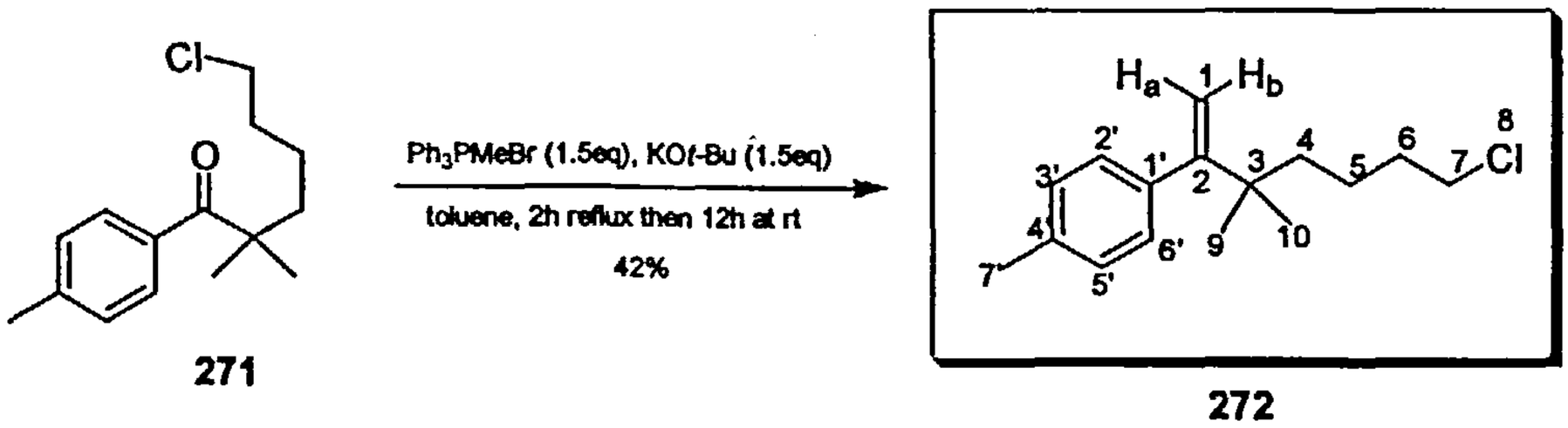


Scheme 67

To a magnetically stirred suspension of sodium amide (0.47 g, 11.96 mmol) in toluene (50 mL) was added 2-methyl-1-*p*-tolyl-propan-1-one **269** (0.97 g, 5.98 mmol) and the reaction left to reflux for 3 hours. The resulting yellow suspension was then cooled to 60°C and to this was added 1-chloro-4-iodobutane (1.09 mL, 8.97 mmol) all in one portion. The reaction mixture was then left to stir overnight at 50°C. The resulting off white suspension was then quenched with saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with diethyl ether (25 mL x 3) and the combined organic extracts were washed with brine and dried over magnesium sulphate. Evaporation of the solvent under reduced pressure and purification by flash column chromatography (hexane) gave **271** as a colourless oil (0.62 g, 41%); R_f 0.5 (diethyl ether/ hexane 1:9); ν_{max} (neat)/cm^{-1} 2956 (s), 2341 (w), 1669 (s), 1608 (s), 1471 (s), 1174 (s), 968 (s), 827 (s); δ_H (360 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.2, 2', 6'-H), 7.20

(2H, d, *J* 8.0, 3', 5'-H), 3.47 (2H, t, *J* 6.7, 6-H), 2.39 (3H, s, 7'-H), 1.78-1.67 (4H, m, 5-H), 1.40-1.34 (2H, m, 3-H), 1.32 (6H, s, 9, 10-H); δ_C (90 MHz, $CDCl_3$) 208.5 (1-C), 141.0 (4'-C), 136.3 (1'-C), 129.2 (3', 5'-C), 128.4 (2', 6'-C), 48.0 (2-C), 45.1 (6-C), 40.8 (3 or 5-C), 33.5 (3 or 5-C), 26.7 (9, 10-C), 22.7 (4-C), 21.9 (7'-C); *m/z* (EI) 254 ($[M+2H]^+$; 4), 253 ($[M+H]^+$; 11), 252 (M^+; 35), 217 (5), 162 (69), 120 (100), 91 (94), 65 (46), 41 (42).

7-Chloro-3, 3-dimethyl-2-*p*-tolyl-hept-1-ene (272).



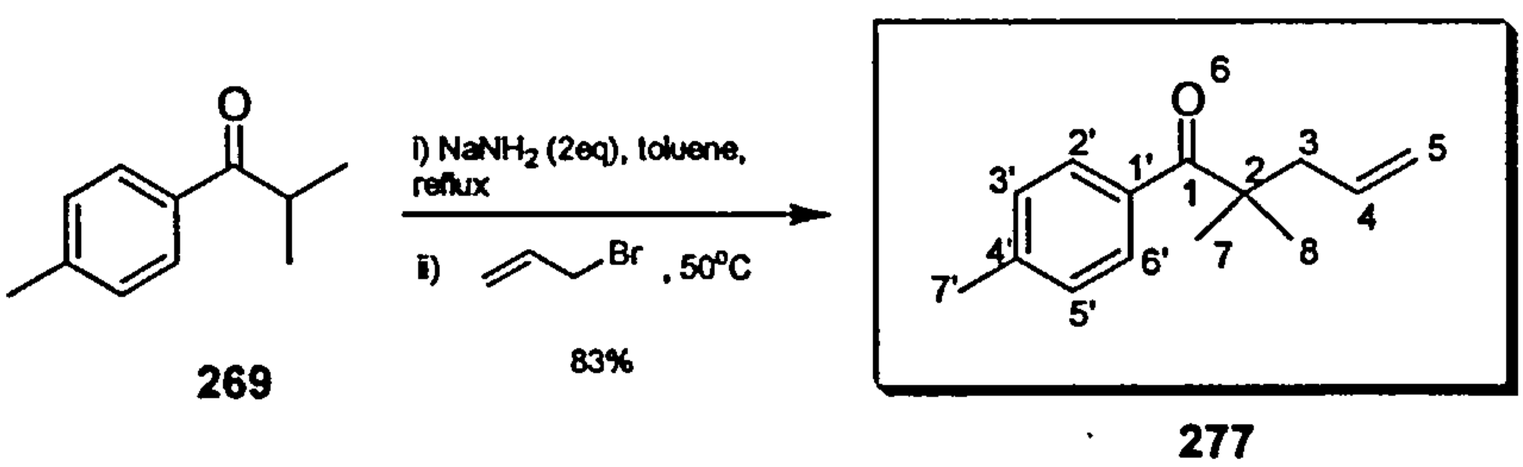
271 **272**

Scheme 68

Potassium tert-butoxide (0.40 g, 3.56 mmol), methyltriphenylphosphonium bromide (1.27 g, 3.56 mmol) and toluene (15 mL) were placed in a 100 mL two neck round bottom flask, fitted with a condenser and under an argon atmosphere. The mixture was refluxed with stirring for 1.5 hours at which point it became bright yellow. To this was added a solution of 6-Chloro-2, 2-dimethyl-1-*p*-tolyl-hexan-1-one **271** (0.6 g, 2.37 mmol) in toluene (10 mL) dropwise at ~35°C. The resulting orange mixture was then refluxed for a further 2 hours and then left to at room temperature overnight. The reaction mixture was diluted with hexane (20 mL) and water (10 mL), stirred for a further 5 minutes and the organic layer was separated from the aqueous. The aqueous

layer was washed with hexane (10 mL x2) and the combined organic layers were cooled to 0°C. The precipitated triphenylphosphine oxide was filtered and the filtrate was rotary evaporated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography (diethyl ether/hexane 0.5:9.5) to afford the title compound as a colourless oil (0.25 g, 42%); R_f 0.77 (diethyl ether/ hexane 1:4); δ_H (360 MHz, $CDCl_3$) 7.09 (2H, d, J 8.0, 2', 6'-H), 7.01 (2H, d, J 8.0, 3', 5'-H), 5.11 (1H, d, J 1.6, 1-H_a), 4.85 (1H, d, J 1.6, 1-H_b), 3.52 (2H, t, J 6.7, 7-H), 2.34 (3H, s, 7'-H), 1.82-1.68 (2H, m, 4-H), 1.48-1.40 (2H, m, 5 or 6-H), 1.33-1.26 (2H, m, 5 or 6-H), 1.09 (6H, s, 9, 10-H); δ_C (90 MHz, $CDCl_3$) 157.4 (2-C), 140.3 (4'-C), 135.9 (1'-C), 128.7 (3', 5'-C), 128.1 (2', 6'-C), 113.5 (1-C), 45.1 (7-C), 40.0 (4-C), 39.2 (3-C), 33.4 (5 or 6-C), 27.7 (9 or 10-C), 22.2 (5 or 6-C), 21.1 (7'-C); m/z (EI) 252 ($[M+2H]^+$; 2), 251 ($[M+H]^+$; 1), 250 (M^+; 5), 194 (7), 160 (100), 145 (29), 128 (20), 117 (33), 115 (26), 114.5 (0.4), 105 (30), 91 (17), 57.5 (0.3), 55 (19).

2,2-Dimethyl-1-*p*-tolyl-pent-4-en-1-one (277).

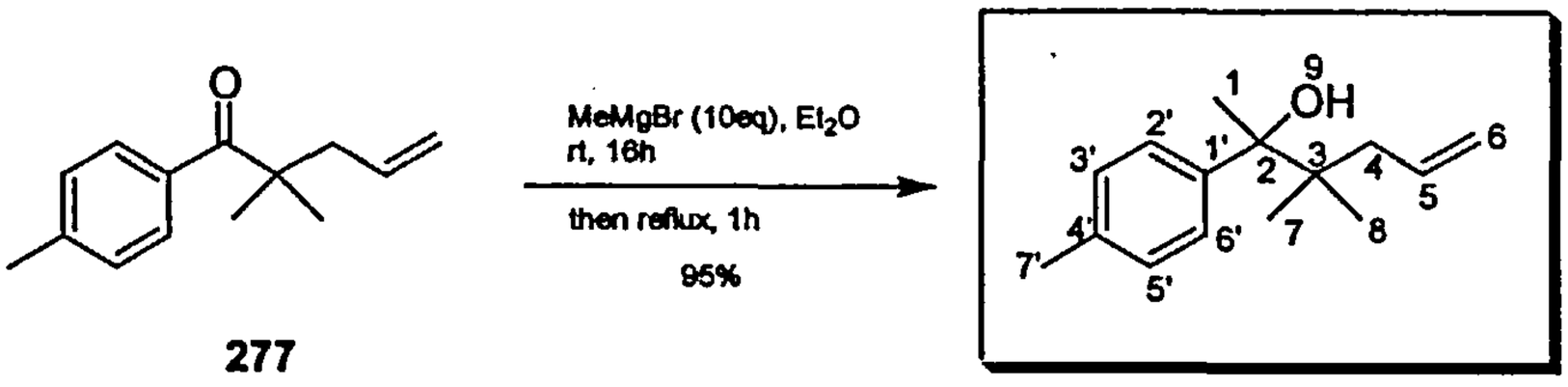


Scheme 72

To a magnetically stirred suspension of sodium amide (0.9 g, 22.8 mmol) in toluene (80 mL) was added 2-methyl-1-*p*-tolyl-propan-1-one **269** (1.85 g, 11.4 mmol) and the reaction left to reflux for 3 hours. The resulting yellow suspension was then cooled to 50°C and to this was added allyl bromide (2.96 mL, 34.3 mmol) all in one portion. The reaction mixture was then left to stir overnight at 50°C. The resulting white suspension was then quenched with saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with benzene (50 mL x 3) and the combined organic extracts were washed with brine and dried over magnesium sulphate. Evaporation of the solvent under reduced pressure and purification by flash column chromatography (diethyl ether/ hexane 1:9) gave the keto-alkene **277** as a colourless oil (1.92 g, 83%); Analytical data agree with that reported in the literature[132]; R_f 0.47 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 1672 (s, C=O), 1608 (s), 918 (m), 827 (m), 755 (m); δ_H (360 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.0, 2', 6'-H), 7.21 (2H, d, *J* 8.0, 3', 5'-H), 5.76-5.65 (1H, m, 4-H), 5.04-4.98 (2H, m, 5-H), 2.51-2.49 (2H, m, 3-H), 2.38 (3H, s, 7'-H), 1.32 (6H, s, 7, 8-H); δ_C (90 MHz, $CDCl_3$) 208.2 (1-C), 141.8 (4'-C), 136.3 (1'-C), 134.6 (4-C), 129.1 (3', 5'-C), 128.5 (2', 6'-C), 118.4 (5-C), 47.9 (2-C), 45.5 (3-C),

26.2 (7, 8-C), 21.8 (7'-C); *m/z* (EI) 203 ($[M+H]^+$; 2), 202 (M^+, 10), 119 (100), 91 (19), 65 (6), 55 (6), 41 (9).

3,3-Dimethyl-2-*p*-tolyl-hex-5-en-2-ol (280).



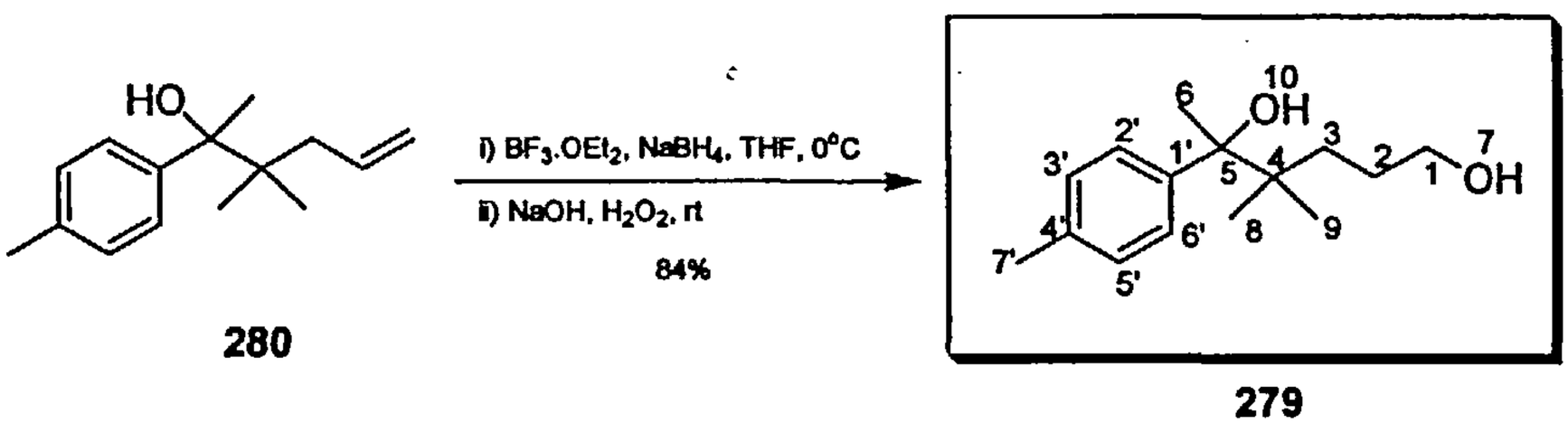
277 **280**

Scheme 73

To an oven dry 100 mL three neck round bottom flask, fitted with a condenser, pressure equalising funnel and argon inlet was added a solution of methylmagnesium iodide (31.7 mL, 3.0M, 95.0 mmol) in ether and the solution cooled to 0°C. To this was added a solution of 2,2-Dimethyl-1-*p*-tolyl-pent-4-en-1-one **277** (1.92 g, 9.50 mmol) in diethyl ether (10 mL), dropwise via the pressure equalising funnel and the reaction left to stir at room temperature for 18 hours. The resulting dark brown mixture was then refluxed for 2 hours, cooled to 0°C and then quenched in saturated ammonium chloride. The organic layer was separated and the aqueous phase was extracted with diethyl ether (50 mL x 3). The combined organic phase was washed with brine and dried over magnesium sulphate to yield after rotary evaporation a pale yellow oil. Purification of the residue by flash column chromatography (diethyl ether/ hexane 1:20) furnished the alcohol **280** as a colourless oil (1.97 g, 95%); Analytical data agree with that reported in the literature[132]; R_f 0.37 (diethyl ether/ hexane 1:10); ν_{max} (neat)/cm^{-1} 3482 (bs, OH), 1387 (w), 1372 (m), 1100 (s), 910 (s), 820 (s); δ_H (360 MHz, $CDCl_3$) 7.33 (2H, d, *J* 8.2,

2', 6'-H), 7.12 (2H, d, *J* 8.0, 3', 5'-H), 5.89-5.79 (1H, m, 5-H), 5.04-4.96 (2H, m, 6-H), 2.34 (3H, s, 7'-H), 2.17-2.02 (2H, m, 4-H), 1.69 (1H, s, 9-H), 1.59 (3H, s, 1-H), 0.89 (3H, s, 7 or 8-H), 0.88 (3H, s, 8 or 7-H); δ_C (90 MHz, $CDCl_3$) 143.0 (4'-C), 136.5 (5-C), 135.9 (1'-C), 127.9 (3', 5'-C), 127.2 (2', 6'-C), 117.0 (6-C), 79.0 (2-C), 41.9 (4-C), 40.8 (3-C), 25.4 (1-C), 22.4 (7 or 8-C), 22.1 (8 or 7-C), 20.9 (7'-C); *m/z* (EI) 218 (M^+; 1), 177 (3), 135 (100), 119 (18), 91 (9), 55 (10), 43 (69).

4,4-Dimethyl-5-*p*-tolyl-hexan-1,5-diol (279).



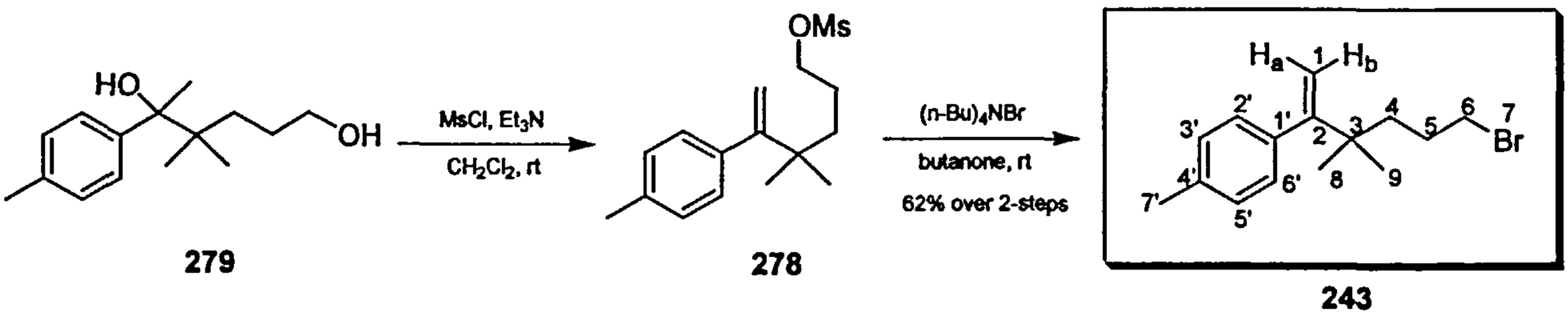
280 **279**

Scheme 74

To a magnetically stirred suspension of $NaBH_4$ (3.79 g, 100.21 mmol) in THF (130 mL) was added $BF_3.OEt_2$ (11.2 mL, 91.41 mmol) dropwise at 0°C. The mixture was stirred for 2 hours at room temperature to ensure complete formation of the hydroborating agent and then cooled back to 0°C. To the cold mixture was added 3,3-Dimethyl-2-*p*-tolyl-hex-5-en-2-ol **280** (5.81 g, 26.65 mmol) in THF (20 mL) dropwise and the reaction stirred at room temperature for 4 hours. The reaction mixture was then cooled to 0°C and H_2O (52 mL), NaOH (32 mL) and H_2O_2 (32 mL) were introduced sequentially and the mixture left to stir overnight. To the reaction mixture was added diethyl ether (100 mL) and the organic layer separated. The aqueous layer was

extracted with ether (100 mL x 3) and the combined organic layers were washed with brine and dried over magnesium sulphate. Evaporation of the solvent and purification by flash column chromatography (diethyl ether/ hexane 1:1) furnished the diol **279** (5.27 g, 84%) as a colourless oil which solidified in the freezer; Analytical data agree with that reported in the literature[132]; R_f 0.1 (diethyl ether/ hexane 1:9); δ_H (360 MHz, $CDCl_3$) 7.33 (2H, d, J 8.2, 2', 6'-H), 7.12 (2H, d, J 7.9, 3', 5'-H), 3.56 (2H, t, J 6.6, 1-H), 2.33 (3H, s, 7'-H), 1.70 (1H, bs, 10-H), 1.58 (3H, s, 6-H), 1.52-1.36 (5H, m, 2, 3, 7-H), 0.89 (3H, s, 8 or 9-H), 0.88 (3H, s, 9 or 8-H); δ_C (90 MHz, $CDCl_3$) 143.7 (4'-C), 136.3 (1'-C), 128.3 (3', 5'-C), 127.6 (2', 6'-C), 79.5 (5-C), 64.4 (1-C), 40.6 (4-C), 33.0 (2-C), 28.5 (3-C), 25.8 (6-C), 22.2 (8, 9-C), 21.3 (7'-C); m/z (EI) 236 (M^+; 3), 135 (91), 119 (78), 105 (24), 91 (78), 83 (21), 69 (35), 65 (56), 55 (50), 43 (100).

6-Bromo-3,3-dimethyl-2-*p*-tolyl-hex-1-ene (243).



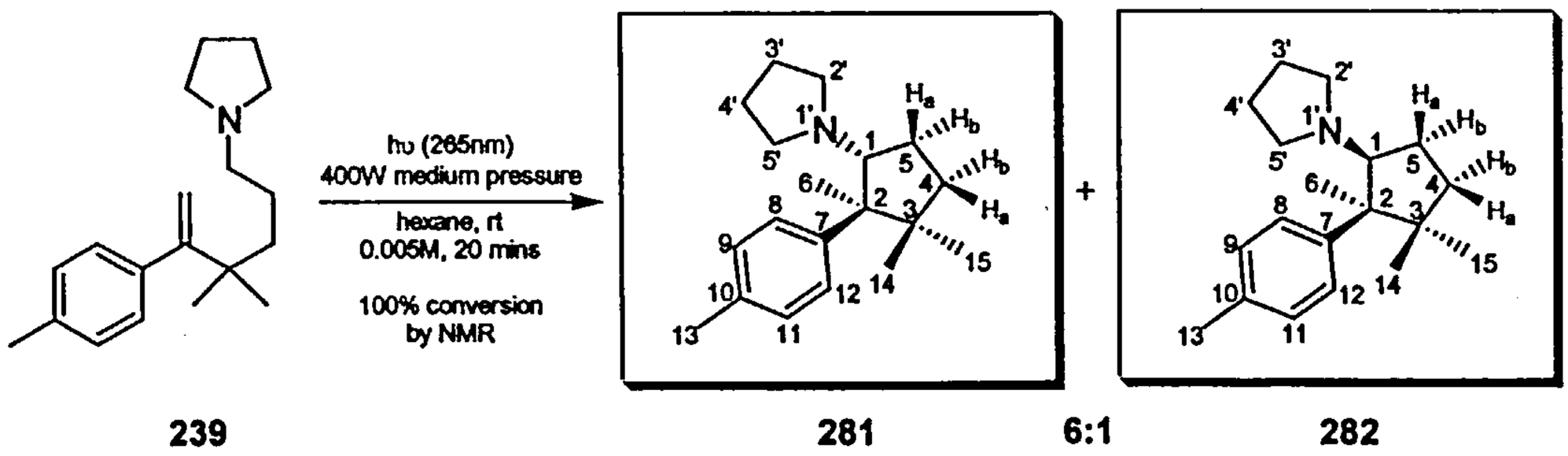
Scheme 75

To a cold (-10°C) magnetically stirred solution of 4,4-Dimethyl-5-*p*-tolyl-hexan-1,5-diol **279** (1.2 g, 5.08 mmol) and triethylamine (12.7 mL, 91.52 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (15.6 mL, 200.97 mmol) dropwise over 30 minutes and the reaction left to stir at room temperature for 16 hours

(under an argon atmosphere). The resulting orange/brown solution was then poured into aqueous HCl (100ml, 1M) and extracted with dichloromethane (50 mL x 3). The dichloromethane extract was washed with saturated sodium hydrogen carbonate and brine. The organic layer was dried over magnesium sulphate and rotary evaporated to afford the crude mesylate **278** (1.5 g, 100%) as a yellow oil which was used without further purification.

To a solution of mesylate **278** (1.50 g, 5.08 mmol) in butan-2-one (20 mL) was added tetra-n-butyl ammonium bromide (2.92g, 9.08mmol), carried out in a 50ml two neck round bottom flask equipped with an argon inlet and magnetic stirrer. The resulting orange/brown homogenous mixture was left to stir for 16hours at room temperature. Once reaction was complete by tlc the butan-2-one was removed under reduced pressure and the residue was taken up in DCM (50ml). The organic phase was washed with $NaHCO_3$ (x2), brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an orange oil which was purified by flash column chromatography (hexane) to furnish alkyl bromide **243** as a colourless oil (0.89 g, 63% over 2 steps); Analytical data agree with that reported in the literature[132]; R_f 0.86 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 1512 (m), 908 (s), 825 (s), 730 (m); δ_H (360 MHz, $CDCl_3$) 7.10 (2H, d, *J* 8.0, 2', 6'-H), 7.02 (2H, d, *J* 8.0, 3', 5'-H), 5.12 (1H, d, *J* 1.6, 1-H_a), 4.87 (1H, d, *J* 1.6, 1-H_b), 3.34 (2H, t, *J* 6.9, 6-H), 2.34 (3H, s, 7'-H), 1.93-1.84 (2H, m, 5-H), 1.49-1.43 (2H, m, 4-H), 1.10 (6H, s, 8, 9-H); δ_C (90 MHz, $CDCl_3$) 157.5 (2-C), 140.5 (4'-C), 136.4 (1'-C), 129.0 (3', 5'-C), 128.6 (2', 6'-C), 114.2 (1-C), 39.9 (6-C), 39.4 (3-C), 34.8 (5-C), 28.9 (8, 9-C), 21.5 (7'-C); m/z (EI) 282 ($[M+H]^+$; 13), 281 (M^+; 3), 280 (14), 160 (100), 145 (32), 131 (35), 117 (46), 105 (29), 91 (18), 41 (24).

(1*RS*, 2*SR*)-1-(2,3,3-Trimethyl-2-*p*-tolyl-cyclopentyl)pyrrolidine (281) and (1*SR*, 2*SR*)-1-(2,3,3-Trimethyl-2-*p*-tolyl-cyclopentyl)pyrrolidine (282).



Scheme 77

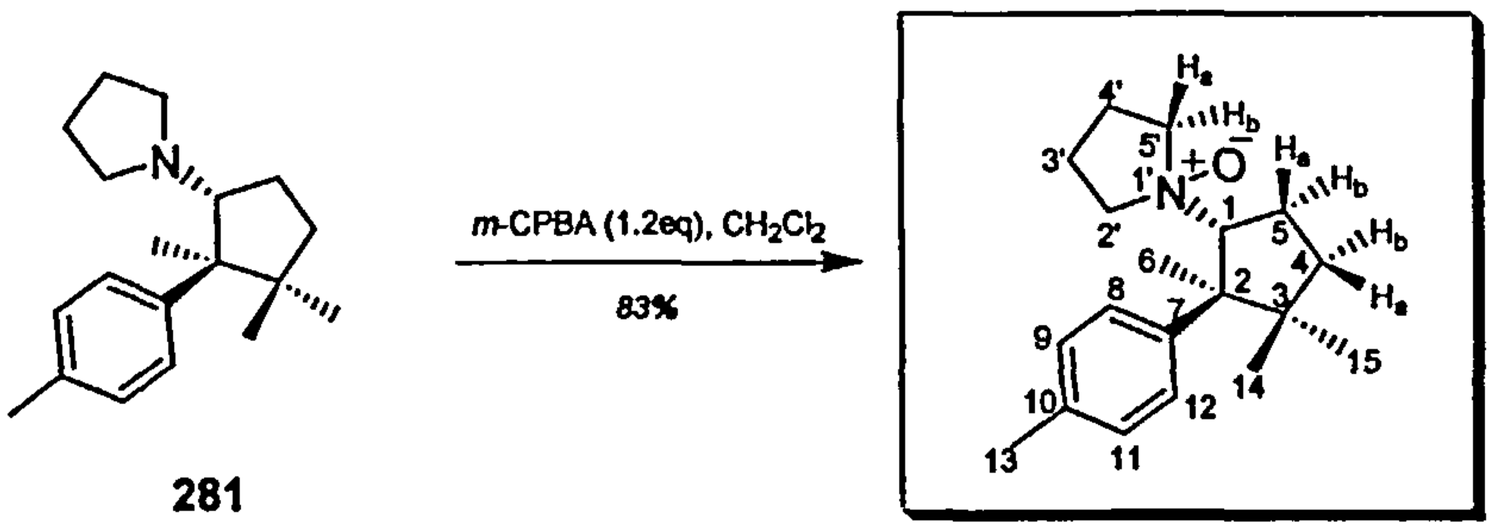
A hexane solution (280 mL, 0.005M) of styryl amine 1-(4,4-dimethyl-5-ρ-tolyl-hex-5-enyl)-pyrrolidine **239** (350 mg, 1.29 mmol) was placed in a quartz vessel and purged with argon for 1 hour. The solution was then irradiated with a medium pressure 400W mercury lamp for 50 minutes. NMR analysis of the irradiated sample showed 100% conversion and the formation of two products **281** and **282** in a 6:1 ratio respectively. After removal of the solvent under reduced pressure, the residue, a deep yellow oil, was chromatographed on silica gel (hexane/diethyl ether 1:1 or hexane/diethyl amine 19:1) to afford diastereomers 281 (215 mg, 62%) and 282 (25 mg, 7%) as pale yellow oils.

Data for **281**: R_f 0.50 (hexane/diethyl amine 19:1); ν_{max} (neat)/cm^{-1} 2957 (s, C-H), 2786 (m), 1515 (m), 1469 (m), 1112 (w), 811 (m); δ_H (360 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.3, 8, 12-H), 6.99 (2H, d, *J* 8.1, 9, 11-H), 3.39 (1H, t, *J* 8.1, 1-H), 2.27-2.20 (2H, m, 2' or 5'-H), 2.25 (3H, s, 13-H), 2.19-2.06 (2H, m, 2' or 5'-H), 2.05-1.98 (1H, m, 5-H_a or 5-H_b), 1.78-1.68 (2H, m, 5-H_a or 5-H_b and 4H_a or 4-H_b), 1.60-1.49 (4H, m, 3', 4'-H), 1.47-1.43 (1H, m, 4-H_a or 4-H_b), 1.29 (3H, s, 6-H), 0.70 (3H, s, 15-H), 0.62 (3H, s, 14-H); δ_C (90 MHz, $CDCl_3$) 141.9 (7-C), 135.7 (10-C), 128.6 (8, 12-C), 128.4 (9, 11-C),

70.2 (1-C), 55.1 (2', 5'-C), 53.8 (2-C), 46.2 (3-C), 38.4 (4-C), 29.3 (5-C), 28.9 (14-C), 24.4 (15-C), 23.9 (3', 4'-C), 21.8 (13-C), 17.3 (6-C); *m/z* (EI) 271 (M^+, 12), 205 (10), 159 (5), 129 (30), 111 (12), 110 (100), 96 (11%); HRMS *m/z* (EI) calculated for $C_{19}H_{29}N$, 271.23001 (M^+), found 271.22939.

Data for **282**: R_f 0.52 (hexane/diethyl amine 19:1); ν_{max} (neat)/cm^{-1} 2968 (s, C-H), 2873 (w), 2778 (m), 1515 (m), 1458 (m), 1085 (m); δ_H (360 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.3, 8, 12-H), 7.01 (2H, d, *J* 8.1, 9, 11-H), 2.75 (1H, dd, *J* 6.7 and 10.2, 1-H), 2.49-2.36 (2H, m, 2' or 5'-H), 2.30 (3H, s, 13-H), 2.24-2.18 (1H, m, 5-H_a or 5-H_b), 2.17-2.07 (2H, m, 2' or 5'-H), 1.95-1.89 (1H, m, 4-H_a or 4-H_b or 5-H_a or 5-H_b), 1.78-1.69 (1H, m, 4-H_a or 4-H_b or 5-H_a or 5-H_b), 1.59-1.47 (5H, m, 3', 4'-H and 4-H_a or 4-H_b or 5-H_a or 5-H_b), 1.01 (3H, s, 15-H), 0.40 (3H, s, 14-H); δ_C (90 MHz, $CDCl_3$) 139.3 (7-C), 132.4 (10-C), 127.3 (8, 12-C), 125.1 (9, 11-C), 74.9 (1-C), 51.8 (2', 5'-C), 51.3 (2-C), 44.7 (3-C), 35.8 (4 or 5-C), 29.5 (5 or 4-C), 23.9 (15-C), 23.1 (14-C), 22.7 (6-C), 21.3 (3', 4'-C), 19.1 (13-C); *m/z* (EI) 271 (M^+, 11), 111 (11), 110 (100), 96 (11%); HRMS *m/z* (EI), calculated for $C_{19}H_{29}N$, 271.23001 (M^+), found 271.22944.

(1*RS*, 2*SR*)-1-(2,3,3-Trimethyl-2-*p*-tolylcyclopentyl)pyrrolidine-1'-oxide (284).



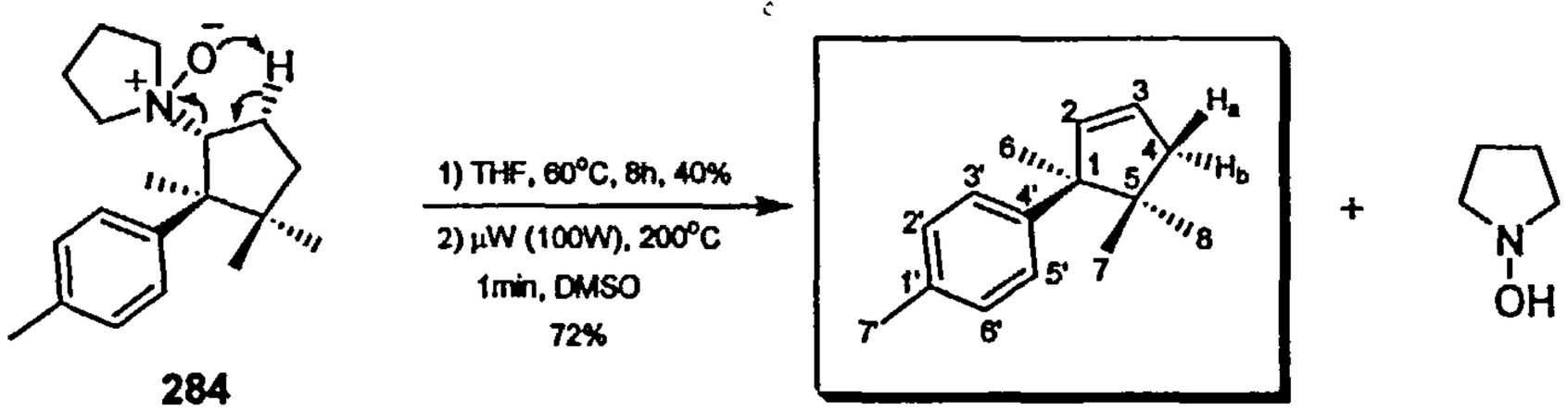
281 284

Scheme 80

To (1*RS*, 2*SR*)-1-(2,3,3-trimethyl-2-*p*-tolyl-cyclopentyl)-pyrrolidine **281** (213 mg, 0.79 mmol) dissolved in dichloromethane (5 mL) at 0°C was added dropwise a solution of *m*-chloroperbenzoic acid (0.16 g, 0.94 mmol) in dichloromethane (3 mL). Once the addition was complete the reaction mixture was brought to room temperature and stired for 3 hours. The reaction was then quenched with $Na_2S_2O_3$ (10 mL, 10%) and washed with saturated aqueous $NaHCO_3$ (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate and the solvent removed in vacuo. The resulting pale brown sticky solid/oil was purified by flash column chromatography (methanol/ethyl acetate 1:1) to yield the pure amine oxide **284** (188 mg, 83%) as a white fluffy sticky solid/oil; R_f 0.17 (methanol/ethyl acetate 1:1); ν_{max} (neat)/cm^{-1} 2924 (s), 2854 (m), 1466 (m, N=O), 1381 (w), 812 (w); δ_H (360 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.5, 8, 12-H), 7.12 (2H, d, *J* 7.9, 9, 11-H), 4.45 (1H, t, *J* 8.9, 1-H), 3.48 (1H, q, *J* 8.5, 5'-H_a or H_b), 3.13-3.09 (1H, m, 5'-H_a or H_b), 3.01-2.98 (1H, m, 5-H_b), 2.93-2.88 (2H, m, 3'-H), 2.36-2.29 (2H, m, 3' or 4'-H), 2.33 (3H,s, 13-H), 2.19-2.13 (1H, m, 5-H_a), 2.02-1.96 (1H, m, 4-H_b), 1.80-1.74 (2H, m, 3' or 4'-H), 1.74 (3H, s, 6-H), 1.65-1.61 (1H, m, 4-H_a), 0.79 (3H, s, 15-H), 0.76 (3H, s, 14-H); δ_C (90 MHz, $CDCl_3$) 139.8 (7-C), 136.1 (10-C), 128.0 (8,

9, 11, 12-C), 79.9 (1-C), 71.8 (5'-C), 67.2 (3'-C), 53.8 (2-C), 46.8 (3-C), 37.0 (4-C), 28.1 (14-C), 23.4 (15-C), 22.5 (3' or 4'-C), 22.2 (5-C), 21.2 (13-C), 21.0 (3' or 4'-C), 18.1 (6-C); *m/z* (FAB) 288 ($[M+H]^+$, 100), 270 (11), (13), 165 (12), 154 (12), 145 (69%); HRMS *m/z* (FAB) calculated for $C_{19}H_{30}NO$, 288.2327 ($[M+H]^+$), found 288.2320.

(1*SR*)-1'-Methyl-4'-(1,5,5-trimethylcyclopent-2-enyl)benzene (283).



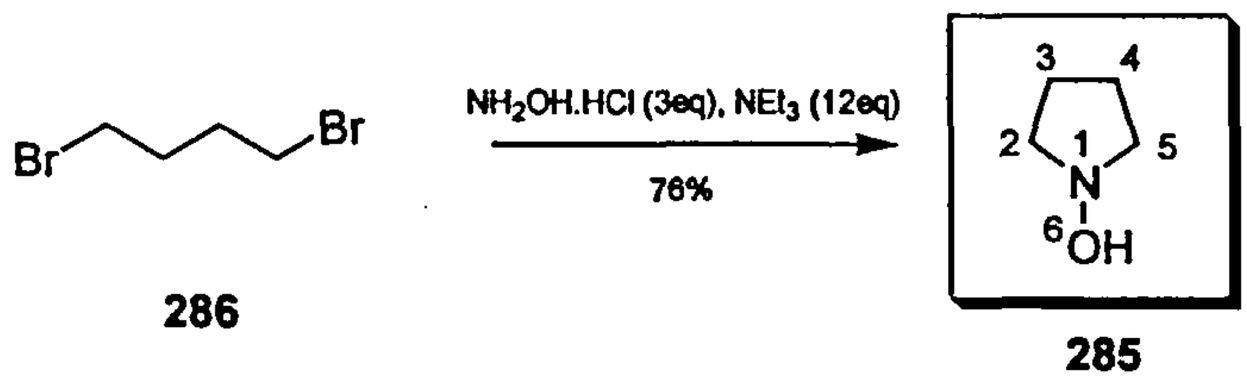
Scheme 81

Method 1: To a 25ml flame dried two neck round bottom flask, under an argon atmosphere was added (1*RS*, 2*SR*)-1-(2,3,3-trimethyl-2-*p*-tolylcyclopentyl)pyrrolidine-1'-oxide **284** (28.5 mg, 0.1 mmol) and THF (4 mL). The colourless solution was then heated to 60°C for 18 hours. The resulting pale yellow solution was cooled to 25°C, concentrated in vacuo and chromatographed over silica gel (hexane) to afford the title compound **283** as a colourless oil (8 mg, 40%).

Method 2: (1*RS*, 2*SR*)-1-(2,3,3-Trimethyl-2-*p*-tolyl-cyclopentyl)-pyrrolidine-1'-oxide **284** (8.6 mg, 0.03 mmol) in deuterated DMSO (0.3 mL) was placed in a microwave

tube. The colourless solution was then irradiated (100W) in the chamber for 1 minute which raised the temperature from 25°C to 200°C. The resulting dark brown solution was then cooled, diluted with diethyl ether (10 mL) and washed with water (2 x 10 mL). The organic layer was removed and the aqueous was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and rotary evaporated to give the crude product. Purification by silica gel chromatography (hexane) afforded **283** as a colourless oil (4.3 mg, 72%); R_f 0.79 (hexane); ν_{max} (thin film)/cm^{-1} 3052 (m, C-H), 3024 (m), 2969 (s), 2925 (s), 1514 (s), 1456 (s), 810 (m), 722 (m); δ_H (360 MHz, DMSO) 7.14 (2H, d, J 8.3, 3', 5'-H), 7.08 (2H, d, J 8.1, 2', 6'-H), 5.86-5.84 (1H, m, 2 or 3-H), 5.81-5.79 (1H, m, 3 or 2-H), 2.34-2.29 (1H, m, 4-H_a or 4-H_b), 2.26 (3H, s, 7'-H), 2.18-2.07 (1H, m, 4-H_a or 4-H_b), 1.22 (3H, s, 6-H), 1.09 (3H, s, 8-H), 0.38 (3H, s, 7-H); δ_C (90 MHz, $CDCl_3$) 143.0 (4'-C), 140.6 (2 or 3-C), 135.6 (1'-C), 128.8 (3', 5'-C), 128.8 (2 or 3-C), 127.1 (2', 6'-C), 56.4 (1-C), 47.8 (4-C), 44.8 (5-C), 28.4 (6 or 7 or 8-C), 24.3 (6 or 7 or 8-C), 23.5 (6 or 7 or 8-C), 21.3 (7'-C); m/z (EI) 201 ($[M+H]^+$, 9), 200 (M^+, 49), 186 (7), 185 (36), 157 (100), 143 (23), 128 (12), 105 (11), 84 (20%); HRMS *m/z* (FAB) calculated for $C_{15}H_{20}$, 200.15660 (M^+), found 200.15627.

Pyrrolidin-1-ol (285).

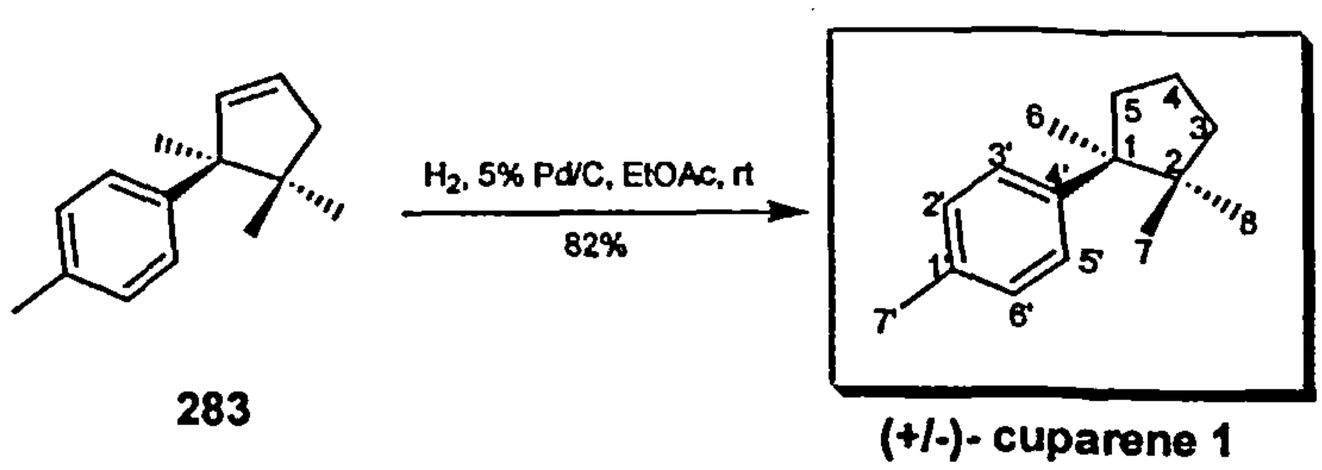


286 **285**

Scheme 82

A solution of 1,4-dibromobutane **286** (1.91 g, 9.12 mmol) in freshly distilled triethylamine (5 mL, 35.9 mmol) was added to a suspension of hydroxylamine hydrochloride (1.73 g, 25.1 mmol) in triethylamine (10 mL, 71.81 mmol). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting white suspension was diluted with dry diethyl ether and filtered through a short pad of celite. Concentration of the solution under reduced pressure gave the crude product **285** as a pale yellow volatile oil, which was sufficiently pure to be used without further purification (600 mg, 75%); Analytical data agree with that reported in the literature[136]; δ_H (360 MHz, $CDCl_3$) 7.75 (1H, bs, 6-H), 3.00 (4H, bs, 2, 5-H), 1.89-1.78 (4H, bm, 3, 4-H).

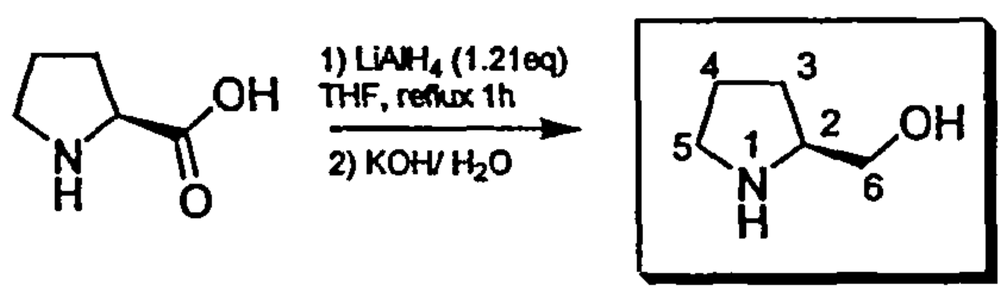
(±)-Cuparene (1).



Scheme 85

To a solution of 1'-methyl-4'-(1,5,5-trimethylcyclopent-2-enyl)benzene **283** (56 mg, 0.28 mmol) in EtOAc (15 mL) was added 5% Pd on charcoal (20 mg). The mixture was stirred under atmospheric hydrogen for 3 hours. The catalyst was removed by filtration through celite and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The resulting yellow oil was purified by flash column chromatography (hexane) to afford the title compound as a colourless oil (46.5 mg, 82%); Analytical data agree with that reported in the literature[4, 5, 7d]; R_f 0.66 (hexane); ν_{max} (neat)/cm^{-1} 3094 (w), 3061 (w), 3025 (w), 2969 (s), 2874 (s), 2727 (w), 1898 (w), 1790 (w), 1516 (s), 1459 (s), 1374 (s), 1193 (m), 1135 (w), 1108 (w), 1020 (m), 812 (s), 724 (m), 547 (s); δ_H (360 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.2, 3', 5'-H), 7.08 (2H, d, *J* 8.1, 2', 6'-H), 2.53-2.45 (1H, m, 5-H_a or H_b), 2.31 (3H, s, 7'-H), 1.83-1.64 (4H, m, 3,4-H), 1.61-1.43 (1H, m, 5-H_a or H_b), 1.25 (3H, s, 6-H), 1.06 (3H, s, 8-H), 0.56 (3H, s, 7-H); δ_C (90 MHz, $CDCl_3$) 144.9 (4'-C), 135.1 (1'-C), 128.6 (3', 5'-C), 127.3 (2', 6'-C), 50.7 (1-C), 44.6 (2-C), 40.1 (3 or 4 or 5-C), 37.2 (3 or 4 or 5-C), 26.9 (6-C), 24.8 (7 or 8-C), 24.7 (7 or 8-C), 21.3 (7'-C), 20.2 (3 or 4 or 5-C); m/z (EI) 203 ($[M+H]^+$, 7), 202 (M^+, 42), 145 (35), 133 (27), 132 (100), 131 (33), 120 (15), 119 (29), 117 (11), 105 (17%).

(*S*)-2-Hydroxymethylpyrrolidine (295).

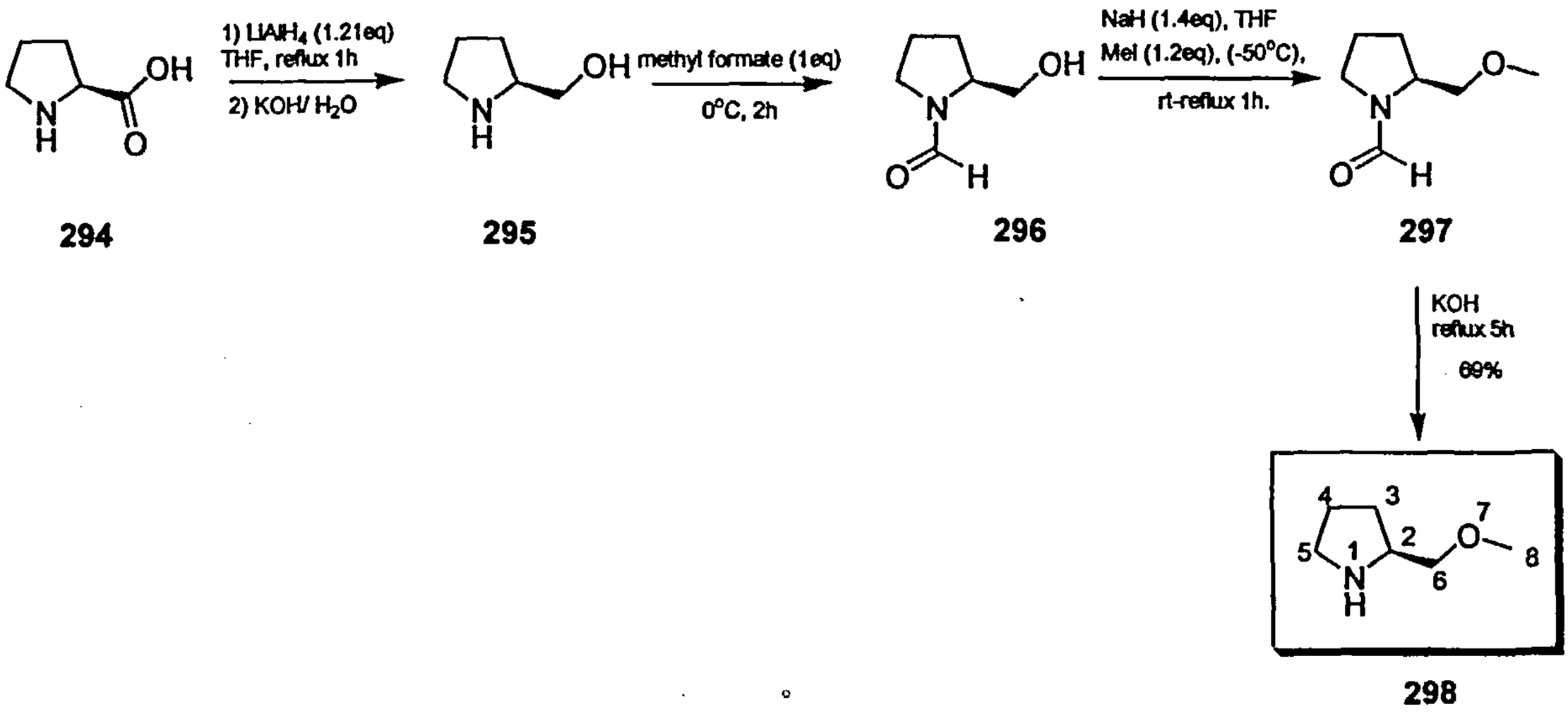


294 **295**

Scheme 86

In a 1L three-neck round bottom flask equipped with a magnetic stirrer, condenser and argon inlet was added $LiAlH_4$ (10 g, 263.5 mmol) and THF (400 mL). The mixture was stirred at room temperature for 5 minutes and then refluxed for 15 minutes. The heating mantle was removed and (*S*)-proline **294** (25 g, 217.2 mmol) was added in small portions and the mixture was heated for 1 hour to reflux. The excess $LiAlH_4$ was decomposed by carefully adding a solution of potassium hydroxide (4.6 g) in water (18.6 mL). After stirring for 15 minutes the mixture was filtered and the salts were transferred to a 250 mL round bottom flask equipped with a condenser and argon inlet. The salts were then extracted with THF (100 mL) under refluxing conditions and filtered. The combined organic filtrates were concentrated under reduced pressure below 30°C to yield the alcohol **295** (26 g) as a yellow/orange liquid.

(*S*)-2-Methoxymethylpyrrolidine (298).



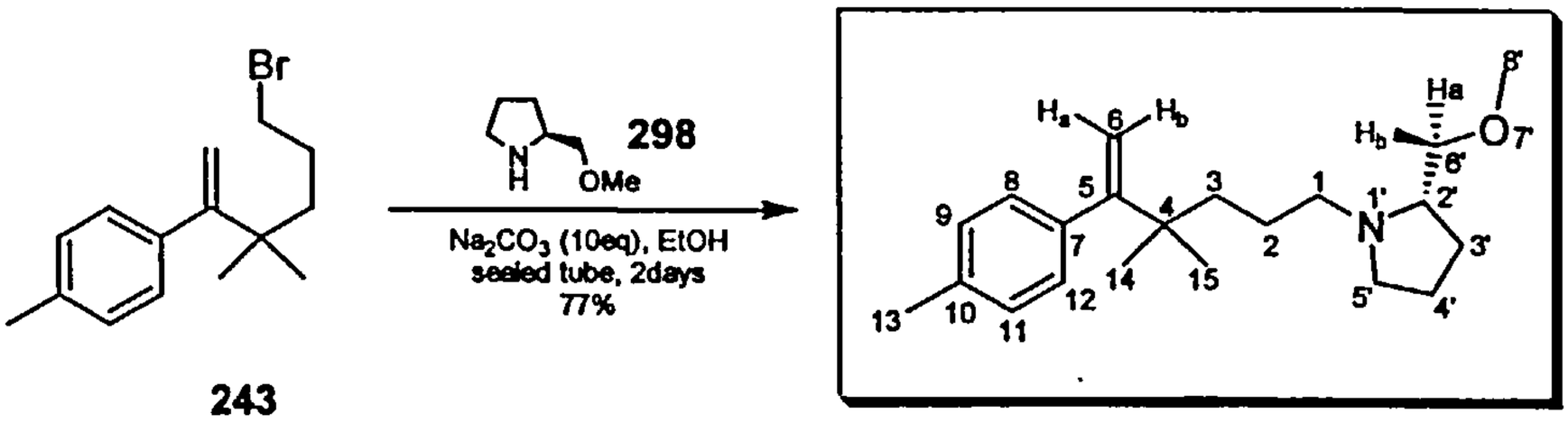
294 295 296 297 298

Scheme 86

The crude alcohol **295** was transferred to a two neck round bottom flask and cooled to 0°C. Methyl formate (13.3 mL, 215.3 mmol) was added dropwise over a period of 1 hour to the crude product and the mixture stirred for 2 hours. Excess methyl formate was removed under reduced pressure at 30°C to afford a dark brown oil. The residue was taken up in dichloromethane (100 mL) and dried over sodium sulphate, filtered and concentrated below 30°C. The resulting *N*-formyl compound **296** was transferred to a three neck round bottom flask equipped with pressure equalising funnel, condenser and argon inlet. Anhydrous THF (250 mL) was added and the solution cooled to –50 to -60°C. To the solution was carefully added methyl iodide (24.8 g, 174.4 mmol) and sodium hydride (60% dispersion 7.7 g, 200 mmol). The solution was allowed to warm to room temperature and then refluxed for 30 minutes. After cooling to room temperature the reaction was quenched with aqueous hydrochloric acid (6M, 10 mL) and filtered. The filtrate was concentrated under reduced pressure to afford a dark orange/brown oil which was then transferred to a 500 mL two neck round bottom flask.

A solution of potassium hydroxide (45 g) in water (150 mL) was added to the crude product with vigorous stirring at room temperature. The mixture was then refluxed for 5 hours and left to stir at room temperature over night. The product **298** was extracted in a 1L perforator over a period of 36 hours with diethyl ether. The organic layer was dried over magnesium sulphate, filtered and concentrated under reduced pressure below 30°C. The residue was distilled at water pump pressure (bp 62°C) to yield the product **298** as a colourless oil (17.2 g, 69% over the 4 steps); Analytical data agree with that reported in the literature[137]; ν_{max} (neat)/cm^{-1} 3330 (bm), 2962 (s), 2873 (s), 2083 (w), 1650 (w), 1458 (m), 1384 (w), 1200 (m), 1104 (s), 972 (w), 921 (m), 814 (m); δ_H (360 MHz, $CDCl_3$) 3.37 (3H, s, 8-H), 3.36-3.30 (1H, m, 2-H), 3.29-3.25 (2H, m, 6-H), 3.00-2.83 (2H, m, 5-H), 2.06 (1H, s, 1-H), 1.88-1.70 (3H, m, 3, 4-H), 1.44-1.35 (1H, m, 3, 4-H); δ_C (90 MHz, $CDCl_3$) 74.8 (6-C), 57.4 (8-C), 56.2 (2-C), 44.9 (5-C), 26.3 (3-C), 23.8 (4-C); *m/z* (EI) 115 (M^+; 3), 84 (1), 83 (2), 82 (2), 71 (6), 70 (100), 68 (5), 56 (2), 55 (6), 44 (6), 43 (9), 41 (6); $[\alpha]_D^{20} = +3$ (neat).

(2*S*)-1-(4,4-Dimethyl-5-*p*-tolyl-hex-5-enyl)-2'-methoxymethylpyrrolidine (286).

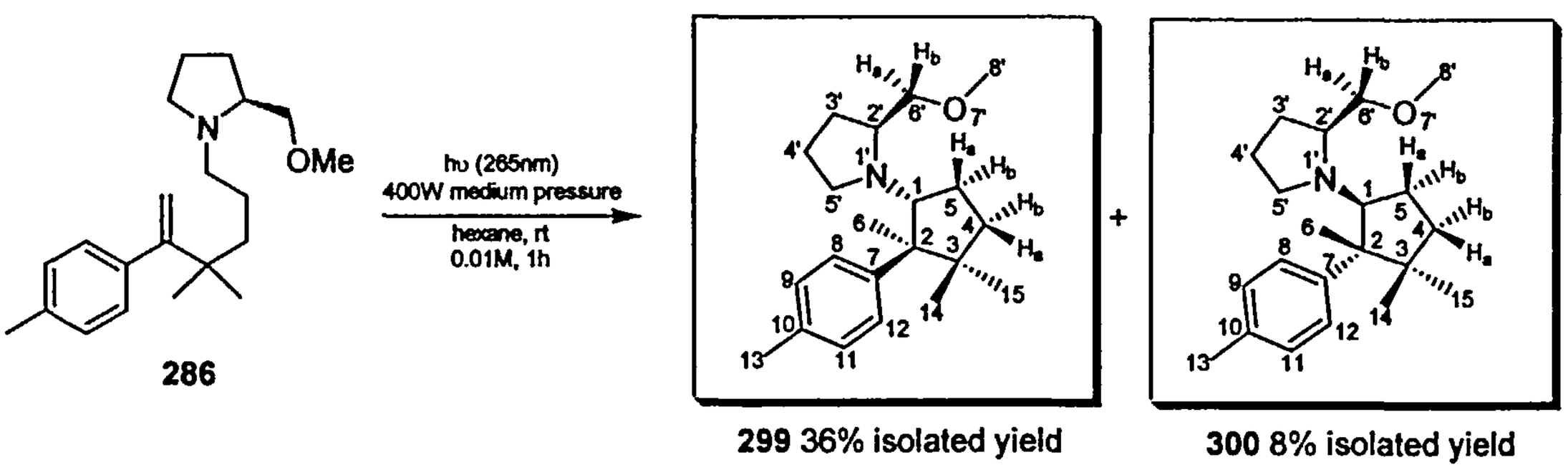


Scheme 87

To a solution of alkyl bromide 243 (123 mg, 0.44 mmol) in absolute ethanol (3 mL) was sequentially added (*S*)-(+)-2-methoxymethylpyrrolidine **298** (74 μL, 0.60 mmol) and anhydrous sodium carbonate (0.47 g, 4.4 mmol). The resulting suspension was heated at 150°C in a sealed tube for 48 hours. The reaction mixture was diluted with EtOAc, filtered, concentrated in vacuo and finally purified by flash column chromatography on silica gel (triethylamine/hexane 1:95) to afford the alkylated product 286 (107 mg, 77%) as a colourless oil; R_f 0.15 (triethylamine/hexane 1:95); ν_{max} (neat)/cm^{-1} 3086 (w), 3023 (w), 2964 (s), 2871 (s), 2806 (m), 1625 (w), 1512 (m), 1459 (m), 1112 (s), 904 (m), 824 (s); δ_H (360 MHz, $CDCl_3$) 7.07 (2H, d, *J* 8.0, 9, 11-H), 7.01 (2H, d, *J* 8.1, 8, 12-H), 5.10 (1H, d, *J* 1.7, 6-H_b), 4.83 (1H, d, *J* 1.7, 6-H_a), 3.40 (1H, dd, *J* 4.7 and 9.3, 6'-H_a or H_b), 3.35 (3H, s, 8'-H), 3.27 (1H, dd, *J* 4.7 and 9.3, 6'-H_a or H_b), 3.17-3.13 (1H, m, 5'-H_a or H_b), 2.78-2.71 (1H, m, 1-H_a or H_b), 2.56-2.49 (1H, m, 2'-H), 2.34 (3H, s, 13-H), 2.25-2.17 (1H, m, 1-H_a or H_b), 2.16-2.11 (1H, m, 5'-H_a or H_b), 1.94-1.60 (4H, m, 3', 4'-H), 1.59-1.43 (2H, m, 2 or 3-H), 1.39-1.26 (2H, m, 2 or 3-H), 1.08 (6H, s, 14-15-H); δ_C (90 MHz, $CDCl_3$) 157.9 (5-C), 140.8 (7-C), 136.1 (10-C), 129.0 (9, 11-C), 128.4 (8, 12-C), 113.8 (6-C), 76.5 (6'-C), 64.1 (2'-C), 59.4 (8'-C), 56.6 (1-C), 54.9 (5'-C), 39.5 (4-C), 38.9 (2 or 3-C), 28.7 (3' or 4'-C), 28.2 (14 or 15-C), 28.0 (15 or 14-C), 24.5 (2 or 3-C),

23.2 (3' or 4'-C), 21.4 (13-C); *m/z* (FAB) 316 ($[M+H]^+$, 96), 315 (M^+, 7), 314 (55), 282 (10), 271 (16), 270 (100), 154 (29), 133 (10), 128 (22), 119 (16), 110 (12), 105 (22%); HRMS *m/z* (FAB calculated for $C_{21}H_{34}NO$, 316.2640 ($[M+H]^+$), found 316.2650; $[\alpha]^{20}_D$ –64.7 (*c* 1.31, $CHCl_3$).

(2'*S*, 1*R*, 2*S*)- 2'-Methoxymethyl–1-(2,3,3-trimethyl-2-*p*-tolyl-cyclopentyl)pyrrolidine (299) and (2'*S*, 1*S*, 2*R*)- 2'-Methoxymethyl-1-(2,3,3-trimethyl-2-*p*-tolyl-cyclopentyl)pyrrolidine (300).



Scheme 88

A hexane solution (280 mL, 0.01M) of styryl amine **286** (1 g, 3.17 mmol) was placed in a quartz vessel and purged with argon for 1 hour. This solution was then irradiated with a medium pressure 400W mercury lamp for 3 hours. NMR analysis of the irradiated sample showed 100% conversion to a mixture of diastereomers in a 10:5:2:1 ratio. After removal of the solvent under reduced pressure, the residue a yellow oil was

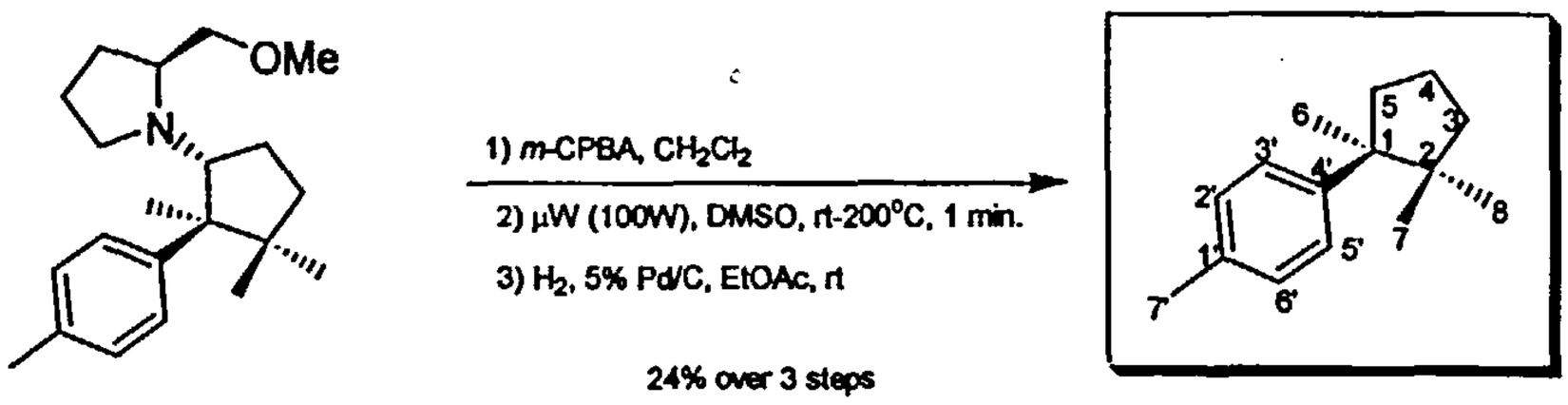
chromatographed on silica gel (hexane-hexane/diethyl ether 1:1). Two major diastereomers were isolated **300** (84 mg, 8%) and **299** (322 mg, 36%) as colourless oils.

Data for **300**: R_f 0.33 (hexane/diethyl amine 19:1); ν_{max} (neat)/cm^{-1} 3060 (w), 2958 (s), 2873 (s), 2822 (s), 2360 (w), 2340 (w), 1515 (m), 1463 (m), 1196 (m), 1113 (s), 811 (m); δ_H (360 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.2, 8, 12-H), 7.05 (2H, d, *J* 8.1, 9, 11-H), 3.96 (1H, t, *J* 8.6, 1-H), 3.36-3.29 (1H, m, 6'-H_a or H_b), 3.33 (3H, s, 8'-H), 3.06-3.00 (2H, m, 6'-H_a or H_b and 2'-H), 2.35-2.26 (1H, m, 5'-H_a or H_b), 2.31 (3H, s, 13-H), 2.19-2.14 (1H, m, 5'-H_a or H_b), 2.11-2.03 (1H, m, 5-H_b), 1.93-1.89 (1H, m, 5-H_a), 1.78-1.74 (1H, m, 4-H_a or H_b), 1.70-1.65 (2H, m, 3'-H), 1.55-1.40 (3H, m, 4-H_a or H_b and 4'-H), 1.30 (3H, s, 6-H), 0.80 (3H, s, 14-H), 0.67 (3H, s, 15-H); δ_C (90 MHz, $CDCl_3$) 142.0 (10-C), 135.0 (7-C), 128.2 (8, 12-C), 127.9 (9, 11-C), 78.2 (6'-C), 68.4 (1-C), 61.9 (2'-C), 59.3 (8'-C), 54.8 (5'-C), 54.0 (2-C), 45.0 (3-C), 38.0 (4-C), 29.0 (3'-C), 28.7 (15-C), 24.5 (4'-C), 24.3 (14-C), 21.3 (13-C), 16.9 (6-C); *m/z* (EI) 315 (M^+, 8), 270 (37), 155 (17), 154 (100), 110 (10%); HRMS *m/z* (EI) calculated for $C_{21}H_{33}NO$, 315.25623 (M^+), found 315.25714; $[\alpha]^{20}_D$ +37.4 (*c* 1.2, $CHCl_3$).

Data for **299**: R_f 0.30 (hexane/diethyl amine 19:1); ν_{max} (neat)/cm^{-1} 2956 (s), 2872 (s), 2824 (m), 2360 (m), 2341 (m), 1515 (m), 1467 (m), 1376 (w), 1196 (w), 1112 (s), 1017 (w), 812 (m); δ_H (360 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.2, 8, 12-H), 7.08 (2H, d, *J* 8.1, 9, 11-H), 4.14 (1H, t, *J* 8.7, 1-H), 3.32 (1H, dd, *J* 8.5 and 4.0, 6'-H_a or H_b), 3.23 (3H, s, 8'-H), 3.15-3.09 (2H, m, 6'-H_a or H_b and 2'-H), 2.60-2.50 (2H, m, 5'-H), 2.31 (3H, s, 13-H), 2.12-2.06 (1H, m, 5-H_a), 1.86-1.77 (1H, m, 5-H_b), 1.75-1.71 (2H, m, 4-H_b and 3' or 4'-H), 1.63-1.49 (4H, m, 4-H_a and 3', 4'-H), 1.30 (3H, s, 6-H), 0.82 (3H, s, 15-H), 0.64 (3H, s, 14-H); δ_C (90 MHz, $CDCl_3$) 141.9 (7-C), 135.1 (10-C), 128.2 (8, 12-C), 128.0 (9, 11-C), 74.8 (6'-C), 65.1 (1-C), 61.8 (2'-C), 59.2 (8'-C), 53.4 (2 or 3-C), 51.1 (5'-C),

44.8 (3 or 2-C), 37.3 (3' or 4'-C), 28.5 (14-C), 27.9 (4-C), 24.5 (5-C), 24.4 (15-C), 24.0 (3' or 4'-C), 21.3 (13-C), 17.4 (6-C); *m/z* (EI) 315 (M^+, 8), 270 (37), 155 (17), 154 (100), 110 (10%); HRMS *m/z* (EI) calculated for $C_{21}H_{33}NO$, 315.25623 (M^+), found 315.25728; $[\alpha]^{20}_D$ –83.9 (*c* 1.22, $CHCl_3$).

(*S*)-(–)-Cuparene (22).

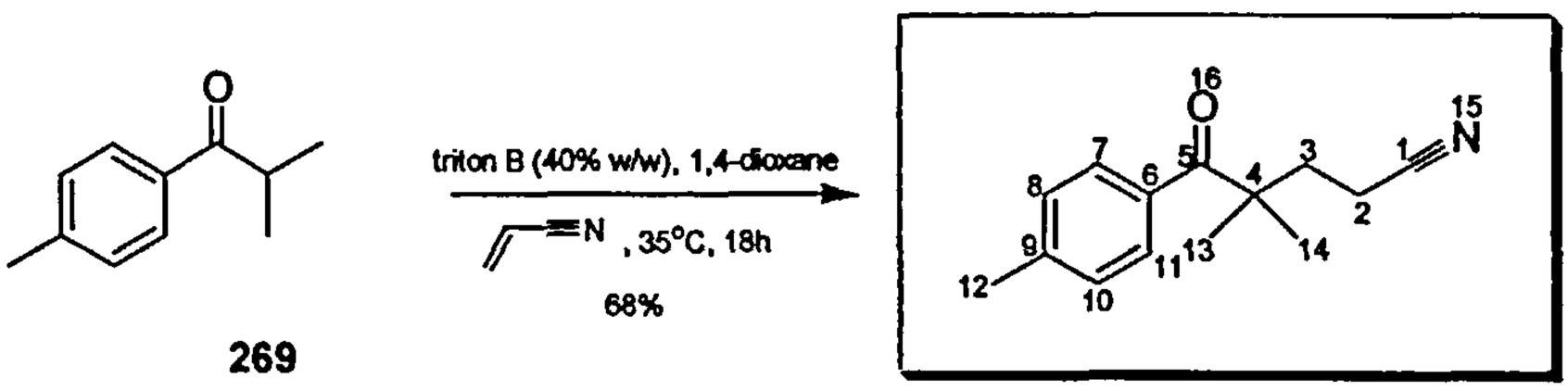


Scheme 89

To (2'*S*, 1*R*, 2*S*)-2'-Methoxymethyl-1-(2,3,3-trimethyl-2-*p*-tolyl-cyclopentyl)pyrrolidine **299** (30 mg, 0.095 mmol) dissolved in dichloromethane (1 mL) at 0°C was added dropwise a solution of *m*-chloroperbenzoic acid (20 mg, 0.11 mmol) in dichloromethane (1 mL). Once the addition was complete the reaction was brought to room temperature and stirred for 3 hours. The reaction was then quenched with $Na_2S_2O_3$ and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried over magnesium sulphate and the solvent removed in vacuo to give the crude amine oxide as a pale brown sticky oil (30 mg). The crude amine oxide (30 mg) was then transferred to a microwave tube using deuterated DMSO (0.8 mL). The pale

yellow solution was then irradiated (100W) in the chamber for 1 minute which raised the temperature to 200°C. The resulting dark brown solution was then cooled, diluted with diethyl ether and washed with water. The organic layer was removed and the aqueous was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and rotary evaporated to give the crude alkene as a orange/brown oil (29.8 mg) which was used in the next step without further purification. To a solution of the crude alkene (29.8 mg) in EtOAc (10 mL) was added 5% Pd on charcoal (12 mg). The mixture was stirred under atmospheric hydrogen for 3 hours. The catalyst was removed by filtration through celite. The combined filtrate and washings were concentrated in vacuo to afford a pale yellow oil, which was purified by flash column chromatography (hexane) to give the title compound as a colourless oil (4.6 mg, 24% over 3 steps); Analytical data agree with that reported in the literature[5, 7d]; R_f 0.66 (hexane); ν_{max} (neat)/cm^{-1} 3094 (m), 3061 (m), 3025 (m), 2969 (s), 2874 (s), 2727 (m), 1898 (m), 1790 (m), 1516 (s), 1459 (s), 1374 (s), 1193 (m), 1135 (w), 1108 (w), 1020 (m); δ_H (360 MHz, $CDCl_3$) 7.23 (2H, d, J 8.2, 3', 5'-H), 7.08 (2H, d, J 8.1, 2', 6'-H), 2.53-2.45 (1H, m, 5-H_a or H_b), 2.31 (3H, s, 7'-H), 1.83-1.64 (4H, m, 3, 4-H), 1.61-1.43 (1H, m, 5-H_a or H_b), 1.25 (3H, s, 6-H), 1.06 (3H, s, 8-H), 0.56 (3H, s, 7-H); δ_C (90 MHz, $CDCl_3$) 144.9 (4'-C), 135.1 (1'-C), 128.6 (3', 5'-C), 127.3 (2', 6'-C), 50.7 (1-C), 44.6 (2-C), 40.1 (3 or 4 or 5-C), 37.2 (3 or 4 or 5-C), 26.9 (6-C), 24.8 (7 or 8-C), 24.7 (7 or 8-C), 21.3 (7'-C), 20.2 (3 or 4 or 5-C); m/z (EI) 203 ($[M+H]^+$, 7), 202 (M^+, 42), 145 (35), 133 (27), 132 (100), 131 (33), 120 (15), 119 (29), 117 (11), 105 (17%); $[\alpha]^{20}_D$ –62.2 (*c* 0.23, $CDCl_3$), lit. $[\alpha]^{20}_D$ –63 (*c* 1.6, $CHCl_3$).

4,4-Dimethyl-5-oxo-5-*p*-tolyl-pentanenitrile (309).

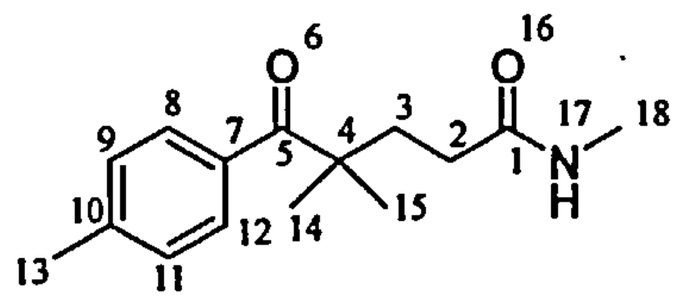


Scheme 92

Acrylonitrile (1.72 g, 32.4 mmol) was added dropwise over 5 minutes to a stirred mixture of 2-methyl-1-*p*-tolyl-propan-1-one **269** (4.8 g, 29.63 mmol), 1,4 dioxane (5 mL) and benzyltrimethylammonium hydroxide (40% w/w, 1.25 g, 2.99 mmol) kept at 30-35°C. The mixture was stirred for a further 18 hours, then acidified using hydrochloric acid, diluted with water and extracted with chloroform (x4). The combined organic extract were freed from dioxane by washing with water, and then dried over magnesium sulphate. The organic phase was concentrated under reduced pressure to give the crude product as a yellow oil. The residue was purified by column chromatography (hexane/diethyl ether 4:1) to afford the title compound **309** as a colourless oil (4.33 g, 68%) and a by-product **313** (75 mg; 1%); R_f 0.27 (hexane/diethyl ether 4:1); ν_{max} (neat)/cm^{-1} 2971 (s), 2875 (m), 2246 (s, nitrile), 1669 (s, C=O), 961 (s), 835 (m); δ_H (360 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.2, 7, 11-H), 7.24 (2H, d, *J* 8.2, 8, 10-H), 2.39 (3H, s, 12-H), 2.31 (2H, dd, *J* 9.0 and 8.9, 2-H), 2.14 (2H, dd, *J* 9.0 and 8.9, 3-H), 1.39 (3H, s, 13, 14-H); δ_C (90 MHz, $CDCl_3$) 206.4 (5-C), 142.8 (6-C), 135.2 (9-C), 129.4 (7, 11-C), 128.6 (8, 10-C), 120.3 (1-C), 47.3 (4-C), 37.0 (3-C), 26.3 (13, 14-C),

21.9 (12-C), 13.5 (3-C); *m/z* (FAB) 216 ($[M+H]^+$; 46), 161 (5), 119 (100%); HRMS *m/z* (FAB) calculated for $C_{14}H_{18}NO$, 216.1388 ($[M+H]^+$), found 216.1394.

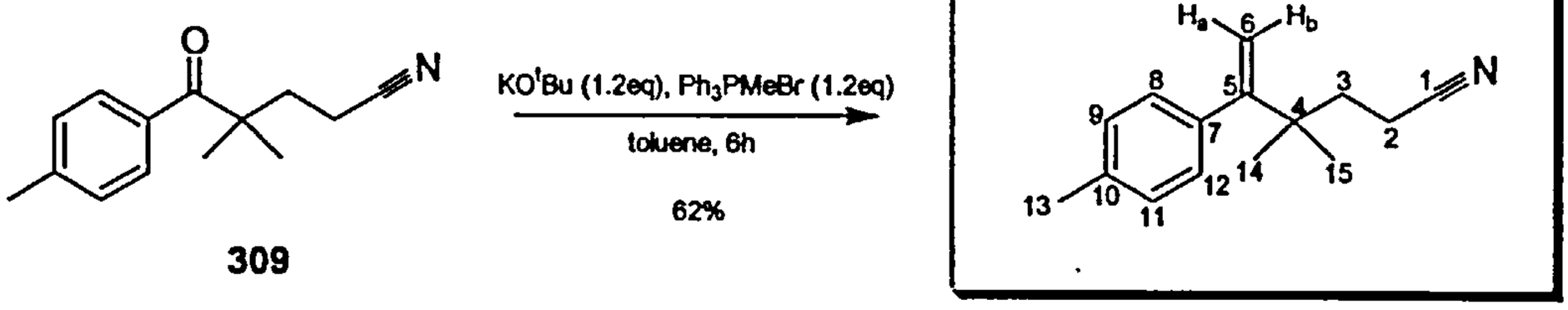
4, 4-Dimethyl-5-oxo-5-p-tolyl-pentanoic acid methylamide (313).



313

ν_{max} (neat)/cm^{-1}) 3449 (bm), 2972 (w), 1735 (m), 1669 (s), 1608 (m), 1436 (w), 1176 (w), 963 (w), 828 (w); δ_H (360 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.2, 8, 12-H), 7.20 (2H, d, *J* 8.1, 9, 11-H), 3.64 (3H, s, 18-H), 2.39 (3H, s, 13-H), 2.29-2.25 (2H, m, 2-H), 2.14-2.11 (2H, m, 3-H), 1.64 (1H, s, 17-H), 1.34 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 207.5 (5-C), 174.3 (1-C), 142.2 (10-C), 135.8 (7-C), 129.3 (9, 11 or 8, 12-C), 128.5 (8, 12 or 9, 11-C), 52.0 (18-C), 47.4 (4-C), 36.1 (3-C), 30.2 (2-C), 26.5 (14, 15-C), 21.8 (13-C).

4,4-Dimethyl-5-*p*-tolyl-hex-5-enenitrile (308).

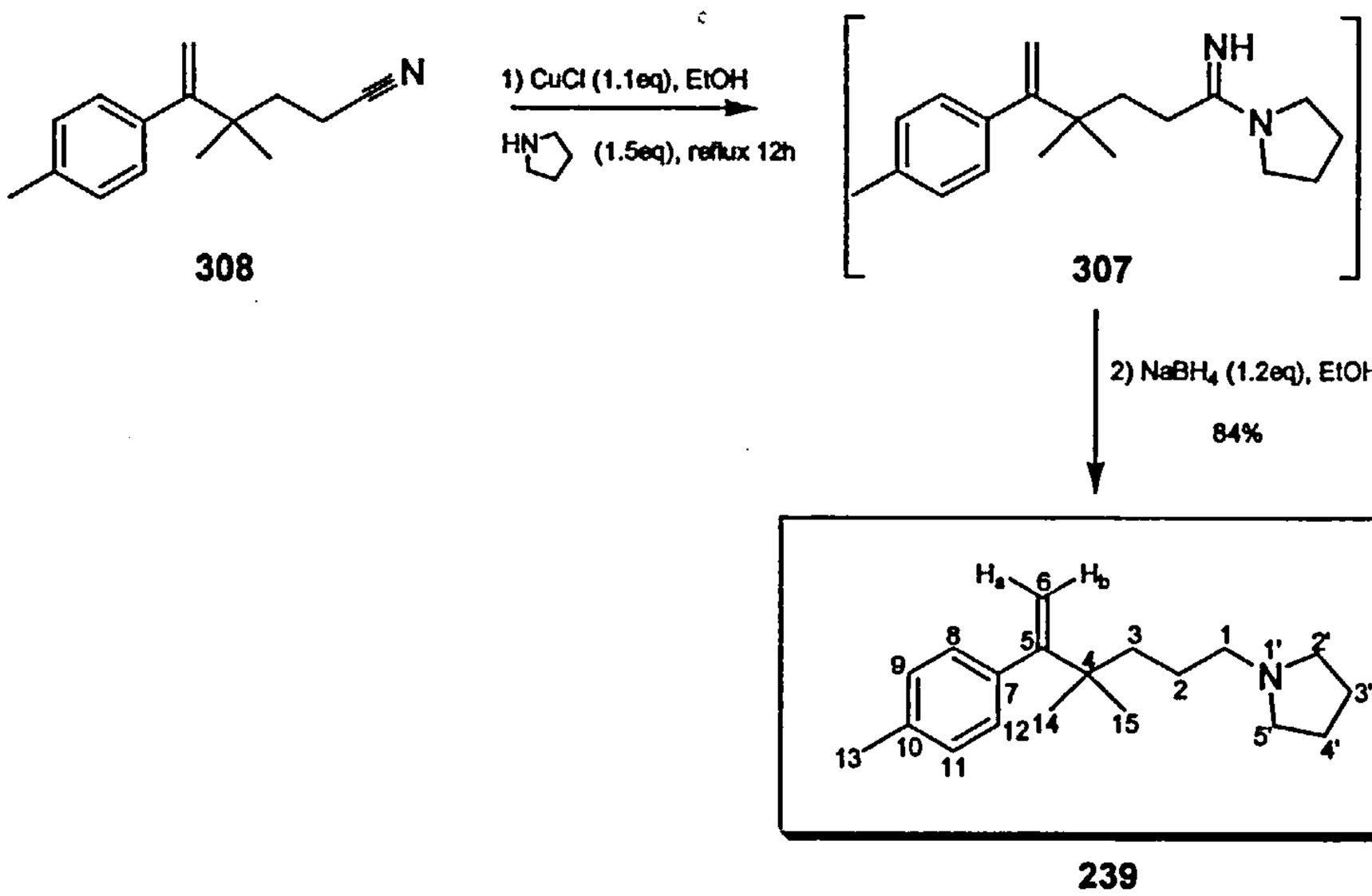


Scheme 94

Potassium *tert*-butoxide (0.77 g, 6.89 mmol), methyltriphenylphosphonium bromide (2.46 g, 6.89 mmol) and toluene (30 mL) were placed in a 100 mL two neck round bottom flask, fitted with a condenser and under an argon atmosphere. The mixture was refluxed with stirring for 2 hours at which point it became bright yellow. To this was added a solution of 4,4-dimethyl-5-oxo-5-*p*-tolyl-pentanenitrile **309** (1.14 g, 5.3 mmol) in toluene (5 mL) dropwise at ~35°C. The resulting brown/orange mixture was then refluxed for a further 6 hours and then left to stir overnight at 40°C for 18 hours. The reaction mixture was diluted with diethyl ether (20 mL) and water (10 mL), stirred for a further 5 minutes and the organic layer was separated from the aqueous. The aqueous layer was washed with diethyl ether (10 mL x2) and the combined organic layers were dried over magnesium sulphate and rotary evaporated to give a yellow oil. The crude product was purified by flash column chromatography (diethyl ether/hexane 1:4) to afford the title compound **308** as a colourless oil (0.7 g, 62%); R_f 0.23 (diethyl ether/hexane 1:4); ν_{max} (neat)/cm^{-1} 2969 (s), 2873 (m), 2246 (s, nitrile), 1626 (m, C=C), 1512 (s), 1384 (s), 911 (s), 826 (s); δ_H (360 MHz, $CDCl_3$) 7.12 (2H, d, *J* 8.0, 8, 12-H), 6.98 (2H, d, *J* 8.0, 9, 11-H), 5.16 (1H, d, *J* 1.2, 6-H_a), 4.96 (1H, d, *J* 1.1, 6-H_b), 2.35

(3H, s, 13-H), 2.33 (2H, dd, *J* 9.8 and 8.3, 2-H), 1.78 (2H, dd, *J* 8.3 and 9.8, 3-H), 1.13 (6-H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 155.8 (5-C), 139.5 (7-C), 136.9 (10-C), 128.9 (8, 12-C), 128.8 (9, 11-C), 120.8 (1-C), 115.5 (6-C), 39.5 (4-C), 36.5 (2-C), 27.6 (14, 15-C), 21.5 (13-C), 13.3 (3-C); *m/z* (FAB) 214 ($[M+H]^+$; 100), 159 (25), 119 (79), 105 (85%); HRMS *m/z* (FAB) calculated for $C_{15}H_{20}NO$, 214.1596 ($[M+H]^+$), found 214.1604.

1-(4,4-Dimethyl-5-*p*-tolyl-hex-5-enyl)pyrrolidine (239).



308 307 239

Scheme 95

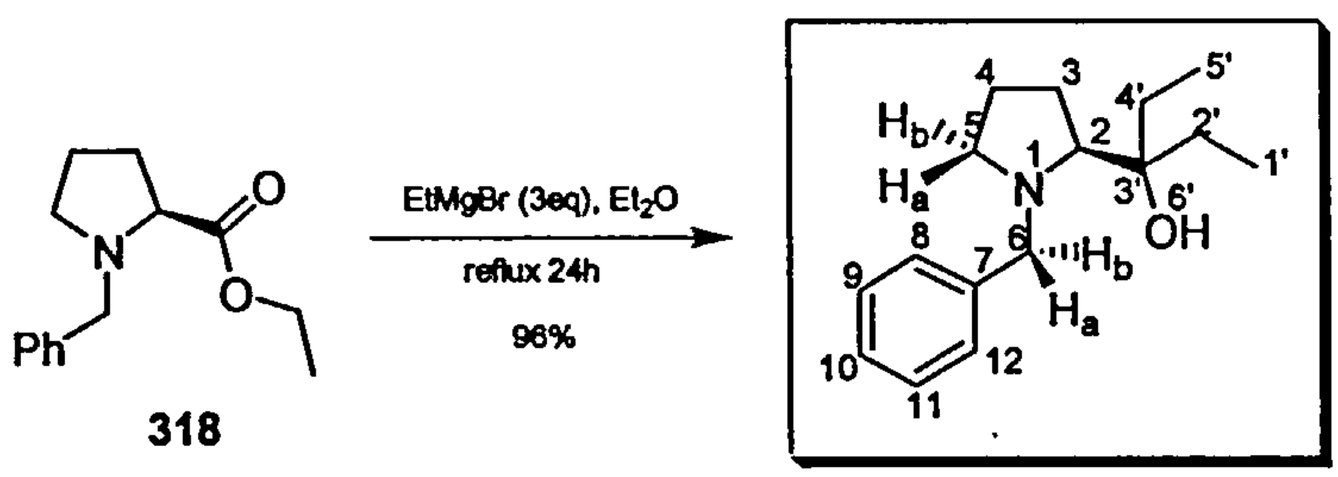
In an oven dried, 25 mL single necked round bottom flask fitted with a condenser and under an argon atmosphere was added 4,4-dimethyl-5-*p*-tolyl-hex-5-enenitrile **308** (0.523 g, 2.46 mmol) and copper (I) chloride (0.27 g, 2.73 mmol). To this was then added a solution of pyrrolidine (306 μL, 3.69 mmol) in ethanol (10 mL) and the

resulting green/brown mixture was then refluxed for 24 hours. The dark brown/red mixture was then cooled down to room temperature and poured with vigorous stirring into a Erlenmeyer flask (100 mL) containing aqueous NaOH (10 mL, 30%) and diethyl ether (20 mL). The mixture was stirred vigorously for 5 minutes. The organic layer was then separated and the aqueous layer was extracted with diethyl ether (x3). The combined organic extracts were dried over magnesium sulphate and rotary evaporated to afford the crude amidine - 4,4-dimethyl-1-pyrrolidine-1-yl-5-*p*-tolyl-hex-5-enylideneamine **307** as a brown oil (0.69 g).

The crude amidine **307** (0.69 g, 2.43 mmol) was then transferred to an oven dried 25 mL two neck round bottom flask, equipped with a magnetic stirrer bar and under an argon atmosphere. To this was then added ethanol (10 mL) via syringe and the reaction mixture cooled to 0°C. Sodium borohydride (0.11 g, 2.95 mmol) was then added with stirring in small portions. The solution was then left to stir at room temperature for 12 hours. Upon completion the mixture was poured into an Erlenmeyer flask (100 mL) containing NaOH (10 mL, 30%) and diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (x3). The combined organic extracts were dried over magnesium sulphate, filtered and solvent removed under reduced pressure. The residue (dark brown oil) was purified by column chromatography (hexane/triethylamine 95:5) to afford the title compound **239** (0.56 g, 84%) as a colourless oil; R_f 0.45 (hexane/triethylamine 95:5); ν_{max} (neat)/cm^{-1} 2964 (s), 2873 (m), 2785 (s), 1625 (m, C=C), 1511 (m), 1449 (s), 1380 (s), 904 (s), 835 (s); δ_H (360 MHz, $CDCl_3$) 7.09 (2H, d, *J* 7.9, 8, 12-H), 7.02 (2H, d, *J* 8.1, 9, 11-H), 5.11 (1H, d, *J* 1.7, 6-H_a), 4.84 (1H, d, *J* 1.7, 6-H_b), 2.51-2.46 (4H, m, 2', 5'-H), 2.38 (2H, d, *J* 7.8, 1-H), 2.34 (3H, s, 13-H), 1.79-1.75 (4H, m, 3', 4'-H), 1.58-1.49 (2H, m, 2-H), 1.35-1.30 (2H, m, 3-H), 1.08 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 157.9 (5-C), 140.9 (7-C),

136.2 (10-C), 129.1 (8, 12-C), 128.4 (9, 11-C), 113.8 (6-C), 57.6 (1-C), 54.7 (2', 5'-C), 39.5 (4-C), 39.1 (2-C), 28.2 (14, 15-C), 24.9 (3-C), 23.8 (3', 4'-C), 21.5 (13-C); *m/z* (EI) 271 (M^+, 30), 256 (13), 200 (16), 152 (20), 143 (23), 110 (80), 84 (100%); HRMS *m/z* (EI) calculated for $C_{19}H_{29}N$, 271.22999 (M^+), found 271.2295.

(2*S*)-3'-(1-Benzyl-pyrrolidin-2-yl)-penatan-3'-ol (319).

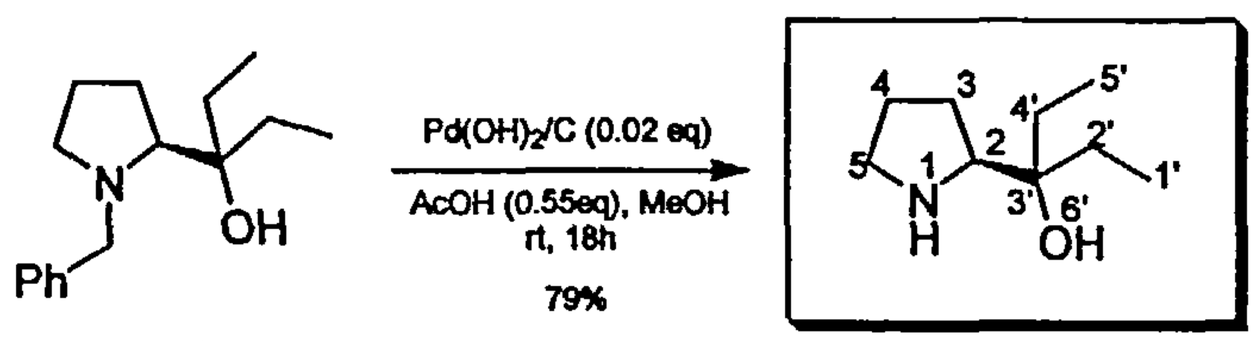


Scheme 96

To an oven dry 100 mL three neck round bottom flask, fitted with a condenser, pressure equalising funnel and argon inlet was added a solution of ethylmagnesium bromide (13.8 mL, 1.0M in THF, 13.76 mmol), diethyl ether (3 mL) and the solution cooled to 0°C. To this was added a solution of N-benzyl-L-proline ethyl ester **318** (1.07 g, 4.59 mmol) in diethyl ether (10 mL), dropwise via the pressure equalising funnel and the reaction left to stir at 0°C for 0.5 hour and room temperature for 1 hour. The pale yellow mixture was then refluxed for 24 hours, cooled to 0°C and then quenched in saturated ammonium chloride. The organic layer was separated and the aqueous phase was extracted with diethyl ether (30 mL x 3). The combined organic phase was washed with brine and dried over magnesium sulphate to yield after rotary evaporation a colourless oil. Purification of the residue by flash column chromatography (diethyl ether/ hexane 1:4) furnished the protected tertiary alcohol **319** as a colourless oil (1.09 g, 96%); Analytical data agree with that reported in the literature[143]; R_f 0.29 (diethyl ether/ hexane 1:4); ν_{max} (neat)/cm^{-1} 3476 (bs), 2965 (s), 2879 (s), 2797 (m), 2360 (w), 1945 (w), 1494 (m), 1452 (m), 1371 (m), 1128 (m), 960 (m), 734 (m), 698 (m); δ_H (360 MHz, $CDCl_3$) 7.40-7.22 (5H, m, 8, 9, 10, 11, 12-H), 4.02 (1H, d, *J* 13.9, 6-H_a or H_b),

3.60 (1H, d, *J* 13.9, 6-H_a or H_b), 2.89 (1H, t, *J* 7.4, 2-H), 2.84-2.53 (2H, m, 5-H_a or H_b and 6'-H), 2.50-2.43 (1H, m, 5-H_a or H_b), 1.84 (2H, q, *J* 7.1, 2' or 4'-H), 1.71-1.55 (5H, m, 2' or 4'-H and 3 or 4-H), 1.43-1.07 (1H, m, 3 or 4-H), 0.89 (3H, dd, *J* 5.9 and 7.5, 1' or 5'-H), 0.87 (3H, dd, *J* 6.2 and 7.5, 1' or 5'-H); δ_C (90 MHz, $CDCl_3$) 140.9 (7-C), 128.7 (8, 12-C), 128.5 (9, 11-C), 127.2 (10-C), 76.4 (3'-C), 70.1 (2-C), 63.5 (5-C), 55.4 (6-C), 29.7 (3 or 4-C), 27.7 (3 or 4-C), 26.4 (2' or 4'-C), 25.5 (2' or 4'-C), 8.5 (1' or 5'-C), 8.2 (1' or 5'-C); *m/z* (EI) 248 ($[M+H]^+$; 10), 230 (8), 160 (100), 91 (17).

(2*S*)-3'-Pyrrolidin-2-yl-pentan-3'-ol (314).

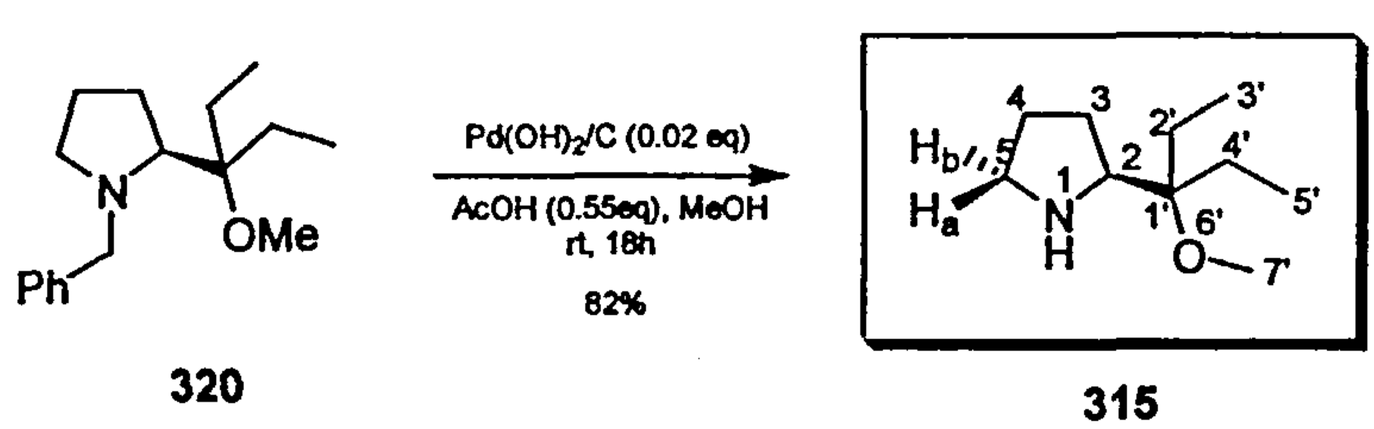


Scheme 96

To a solution of (2*S*)-3'-(1-Benzyl-pyrrolidin-2-yl)-penatan-3'-ol **319** (1.09 g, 4.41 mmol) in methanol (10 mL) was added $Pd(OH)_2$ on carbon (0.05 g, 20 %, 0.08 mmol) and acetic acid (0.15 g, 2.43 mmol). The mixture was then stirred in a hydrogen atmosphere for 18 hours at room temperature. The colourless solution was then filtered through celite and concentrated in *vacuo*. To the residue was added chloroform (30 mL) and this was washed with sodium hydroxide (1M, 30 mL). The organic phase was separated and the aqueous phase was extracted with chloroform (2 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulphate and

rotary evaporated to give a colourless oil. Kugelrohr distillation (60°C, 0.4 mmHg) gave the product as colourless needles (0.55 g, 79%); Analytical data agree with that reported in the literature[143]; ν_{max} (neat)/cm^{-1} 3299 (bw), 1461 (s), 1377 (m), 1133 (w), 965 (m); δ_H (360 MHz, $CDCl_3$) 3.11 (1H, t, *J* 7.8, 2-H), 2.98-2.87 (2H, m, 5-H), 1.80-1.60 (4H, m, 3, 4-H), 1.60-1.32 (4H, m, 2', 4'-H), 0.86 (6H, t, *J* 7.5, 1', 5'-H); δ_C (90 MHz, $CDCl_3$) 74.2 (3'-C), 63.8 (2-C), 46.9 (5-C), 29.8 (3-C), 27.1 (2' or 4'-C), 26.5 (2' or 4'-C), 25.5 (4-C), 8.3 (1' or 5'-C), 8.2 (1' or 5'-C); *m/z* (EI) 158 ($[M+H]^+$; 21), 140 (2), 128 (27), 110 (26), 70 (100).

(2S)-2-(1'-Ethyl-1'-methoxy-propyl)pyrrolidine (315).

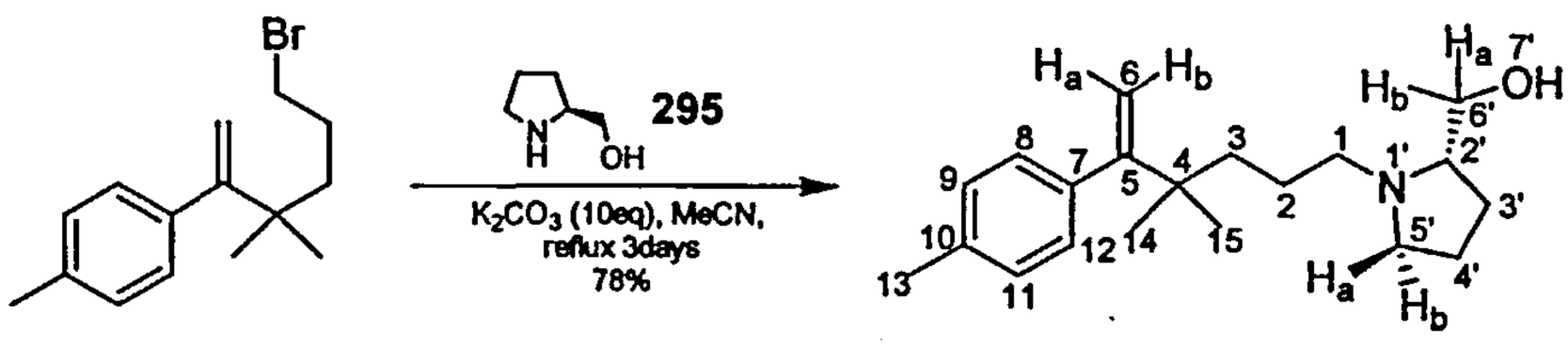


Scheme 97

To a solution of (2*S*)-1-Benzyl-2-(1-ethyl-1-methoxy-propyl)pyrrolidine-2 **320** (1.23 g, 4.71 mmol) in methanol (10 mL) was added $Pd(OH)_2$ on carbon (11.2 mg, 20 %, 0.09 mmol) and acetic acid (0.16 , 2.59 mmol). The mixture was then stirred in a hydrogen atmosphere for 18 hours at room temperature. The colourless solution was then filtered through celite and concentrated in *vacuo*. To the residue was added chloroform (30 mL) and this was washed with sodium hydroxide (1M, 30 mL). The organic phase was separated and the aqueous phase was extracted with chloroform (2 x 20 mL). The

combined organic layers were washed with brine, dried over magnesium sulphate and rotary evaporated to give a colourless oil. Kugelrohr distillation (72°C, 0.4 mmHg) gave the product as white needles (657 mg, 82%); Analytical data agree with that reported in the literature[153]; ν_{max} (neat)/cm^{-1} 3349 (w), 2966 (s), 2942 (s), 2880 (m), 2827 (m), 2360 (w), 1459 (m), 1378 (w), 1084 (s), 926 (w); δ_H (360 MHz, $CDCl_3$) 3.50 (1H, bs, 1-H), 3.29 (3H, s, 7-H), 3.19 (1H, t, *J* 7.9, 2-H), 3.09-2.92 (1H, m, 5-H_a or H_b), 2.90-2.41 (1H, m, 5-H_a or H_b), 1.81-1.49 (8H, m, 4, 3, 2', 4'-H), 0.94 (3H, t, *J* 7.6, 3' or 5'-H), 0.91 (3H, t, *J* 7.6, 3' or 5'-H); δ_C (90 MHz, $CDCl_3$) 79.0 (1'-C), 64.7 (2-C), 50.7 (7-C), 47.1 (5-C), 26.6 (2' or 4'-C), 26.5 (2' or 4'-C), 26.4 (4 or 3-C), 26.0 (4 or 3-C), 8.9 (3', 5'-C); *m/z* (EI) 172 ($[M+H]^+$; 100), 140 (10), 110 (17), 70 (50), 43 (7).

(2'*S*)-[1-(4, 4-Dimethyl-5-*p*-tolyl-hex-5-enyl)-pyrrolidin-2-yl]methanol (288).



243 **288**

Table 3

To a solution of 6-bromo2-*p*-tolyl-hex-1-ene **243** (300 mg, 1.07 mmol) in acetonitrile (10 mL) was sequentially added (*S*)-pyrrolidin-2-yl-methanol **295** (135 μL, 1.39 mmol) and anhydrous potassium carbonate (1.48 g, 10.7 mmol). The resulting suspension was refluxed for 3 days. The mixture was then diluted with ethyl acetate, filtered and concentrated in *vacuo* to give a pale yellow oil. The crude product was purified by flash column chromatography (diethyl ether/ hexane 1:1) to yield amino styrene **288** as a colourless oil (251 mg, 78%); R_f 0.28 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 3424 (bs), 3086 (w), 2949 (s), 2870 (m), 2800 (m), 2428 (w), 1625 (w), 1512 (m), 1451 (s), 1380 (s), 1360 (s), 1112 (m), 1042 (m), 904 (s), 836 (s); δ_H (360 MHz, $CDCl_3$) 7.08 (2H, d, *J* 7.9, 9, 11-H), 7.00 (2H, d, *J* 8.0, 8, 12-H), 5.11 (1H, d, *J* 1.5, 6-H_b), 4.85 (1H, d, *J* 1.5, 6-H_a), 3.59 (1H, dd, *J* 10.6 and 3.6, 6'-H_a or H_b), 3.37 (1H, d, *J* 10.5, 6'-H_a or H_b), 3.18-3.13 (1H, m, 5'-H_a or H_b), 2.80 (1H, bs, 7'-H), 2.64-2.57 (1H, m, 1-H_a or H_b), 2.54-2.49 (1H, m, 2'-H), 2.34 (3H, s, 13-H), 2.27-2.16 (2H, m, 1-H_a or H_b and 5'-H_a or H_b), 1.92-1.70 (4H, m, 3', 4'-H), 1.68-1.43 (2H, m, 2 or 3-H), 1.40-1.35 (1H, m, 2-H_a or H_b or 3-H_a or H_b), 1.29-1.21 (1H, m, 2-H_a or H_b or 3-H_a or H_b), 1.09 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 159.3 (5-C), 142.1 (7-C), 137.5 (10-C), 130.3 (8, 12-C), 129.7 (9,

11-C), 115.1 (6-C), 66.3 (2'-C), 63.4 (6'-C), 56.5 (1-C), 55.8 (5'-C), 40.8 (4-C), 40.2 (2 or 3-C), 29.6 (14 or 15-C), 29.5 (14 or 15-C), 29.3 (3' or 4'-C), 26.0 (2 or 3-C), 25.2 (3' or 4'-C), 22.7 (13-C); *m/z* (FAB) 302 ($[M+H]^+$; 100), 301 (M^+; 7), 300 (32), 284 (5), 271 (13), 270 (65), 154 (7), 140 (16), 133 (6), 114 (13); HRMS *m/z* (FAB) calculated for $C_{20}H_{32}NO$, 302.2484 ($[M+H]^+$), found 302.2490; $[\alpha]_D^{20}$ -31.2 (*c* 1.78, $CHCl_3$).

(2''*S*)-3'-[1-(4, 4-Dimethyl-5-tolyl-hex-5-enyl)-pyrrolidin-2''-yl]pentan-3'-ol (289).

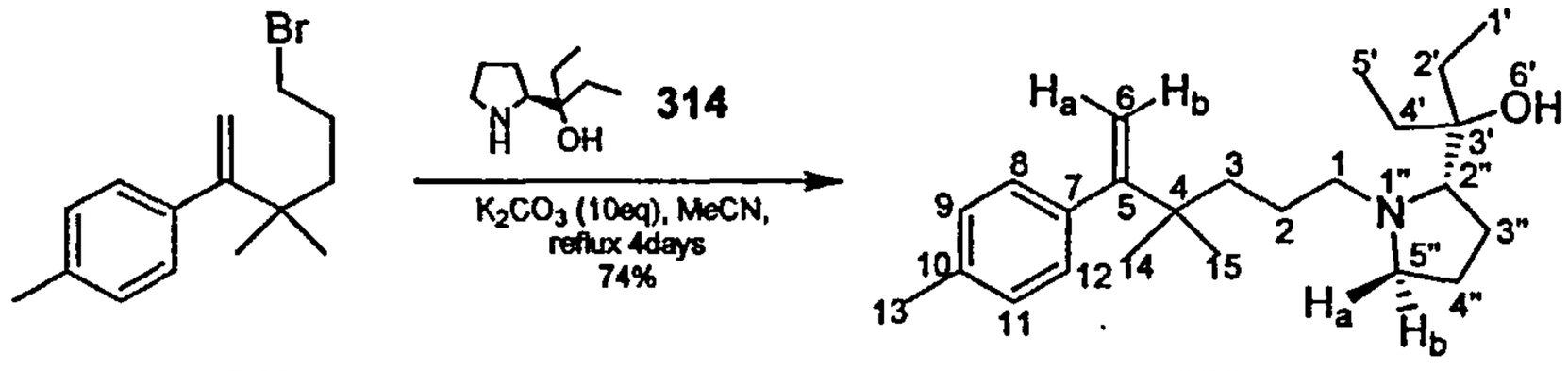
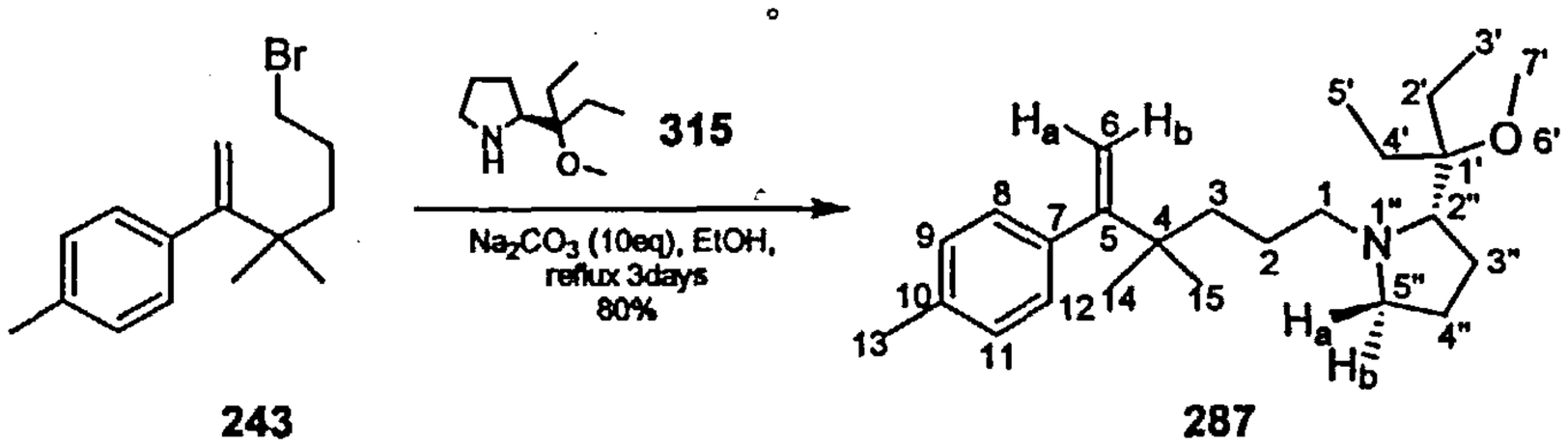


Table 3

To a solution of 6-bromo2-*p*-tolyl-hex-1-ene **243** (200 mg, 0.712 mmol) in acetonitrile (10 mL) was sequentially added (2*S*)-3'-Pyrrolidin-2-yl-pentan-3'-ol **314** (145 mg, 0.93 mmol) and anhydrous potassium carbonate (0.98 g, 7.12 mmol). The resulting suspension was refluxed for 4 days. The mixture was then diluted with ethyl acetate, filtered and concentrated in *vacuo* to give a pale yellow oil. The crude product was purified by flash column chromatography (diethyl ether/ hexane 1:1) to yield amino styrene **289** as a colourless oil (188 mg, 74%); R_f 0.25 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 3473 (bs), 3086 (w), 2965 (s), 2870 (m), 2798 (m), 1626 (w), 1512 (m), 1460 (s), 1379 (m), 1128 (w), 905 (m), 824 (m); δ_H (360 MHz, $CDCl_3$) 7.08 (2H, d, J 7.8, 9, 11-H), 7.00 (2H, d, J 8.0, 8, 12-H), 5.11 (1H, d, J 1.7, 6-H_b), 4.85 (1H, d, J 1.6, 6-H_a), 2.98-2.93 (1H, m, 5''-H_a or H_b), 2.92 (1H, bs, 6'-H), 2.67 (1H, t, J 6.9, 2''-H), 2.69-2.41 (3H, m, 5''-H_a or H_b and 1-H), 2.34 (3H, s, 13-H), 1.77-1.20 (12H, m, 2, 3, 3'', 4'', 2', 4'-H), 1.10 (3H, s, 14 or 15-H), 1.09 (3H, s, 14 or 15-H), 0.84 (6H, q, J 7.4, 1', 5'-H); δ_C (90 MHz, $CDCl_3$) 158.0 (5-C), 140.8 (7-C), 136.3 (10-C), 129.0 (9, 11-C), 128.5 (8, 12-C), 113.8 (6-C), 76.0 (3'-C), 70.5 (2''-C), 60.5 (1-C), 55.4 (5''-C), 39.6 (4-C), 38.6 (2 or 3-C), 29.6 (3'' or 4''-C), 28.3 (14 or 15-C), 28.1 (14 or 15-C), 27.3 (2', 4'-C), 26.4 (2 or 3-C), 25.7 (3'' or 4''-C), 21.5 (13-C), 8.5 (1' or 5'-C), 8.3 (1' or 5'-C);

m/z (FAB) 358 ($[M+H]^+$; 100), 356 (8), 340 (5), 328 (4), 307 (3), 289 (2), 271 (12), 270 (48), 153 (20), 136 (15), 119 (6), 107 (8); HRMS m/z (FAB) calculated for $C_{24}H_{40}NO$, 358.3110 ($[M+H]^+$), found 358.3125; $[\alpha]_D^{20}$ –47.9 (*c* 1.41, $CHCl_3$).

(2''*S*)-1-(4, 4-Dimethyl-5-p-tolyl-hex-5-enyl)-2''-(1'-ethyl-1'-methoxy-propyl)pyrrolidine (287).



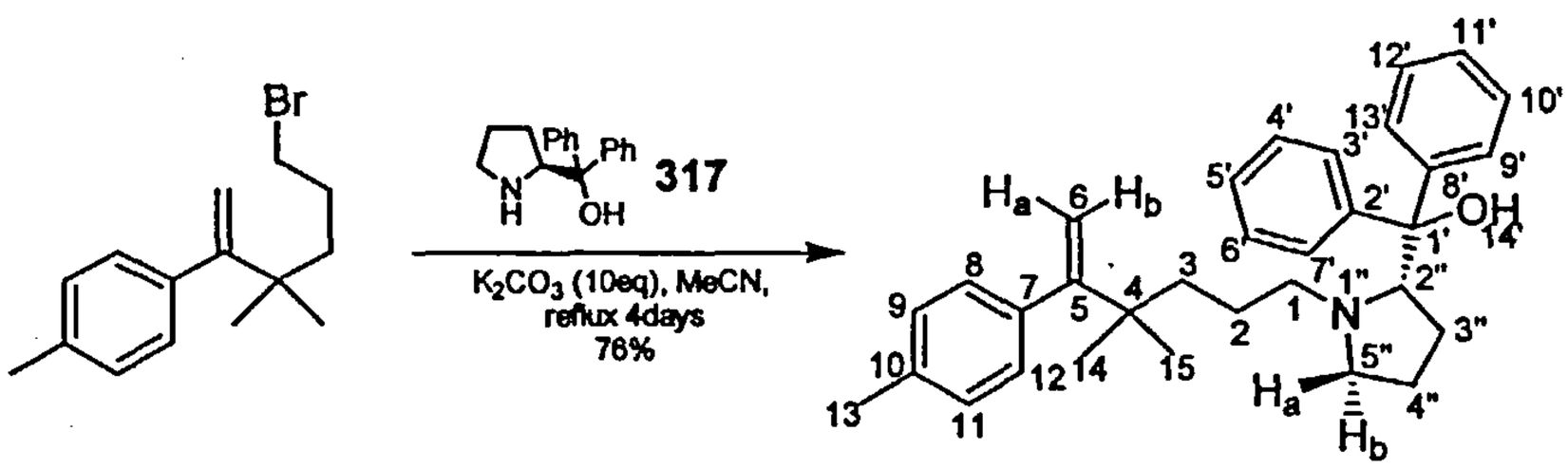
243 **287**

Table 3

To a solution of 6-bromo2-*p*-tolyl-hex-1-ene **243** (413 mg, 1.07 mmol) in absolute ethanol (15 mL) was sequentially added (2*S*)-2-(1'-ethyl-1'-methoxy-propyl)pyrrolidine **315** (301 mg, 1.76 mmol) and anhydrous sodium carbonate (1.56 g, 14.7 mmol). The resulting suspension was refluxed for 3 days. The mixture was then diluted with ethyl acetate, filtered and concentrated in *vacuo* to give a pale yellow oil. The crude product was purified by flash column chromatography (diethyl ether/ hexane 1:1) to yield aminostyrene **287** as a colourless oil (436 mg, 80%); R_f 0.26 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 3022 (w), 2965 (s), 2878 (s), 2766 (m), 2360 (w), 1900 (w), 1810 (w), 1727 (w), 1625 (w), 1512 (m), 1459 (s), 1378 (m), 1088 (s), 904 (m), 823 (m); δ_H (360 MHz, $CDCl_3$) 7.07 (2H, d, J 8.0, 8, 12-H), 7.01 (2H, d, J 8.0, 9, 11-H), 5.11 (1H, d, J

1.7, 6-H_b), 4.83 (1H, d, J 1.7, 6-H_a), 3.26 (3H, s, 7'-H), 3.05-3.01 (1H, m, 5''-H_a or H_b), 2.75-2.70 (1H, m, 5''-H_a or H_b), 2.64 (1H, dd, J 8.0 and 6.0, 2''-H), 2.34 (3H, s, 13-H), 2.25-2.17 (2H, m, 1-H), 1.78-1.20 (12H, 2, 3, 2', 4', 3'', 4''-H), 1.08 (6H, s, 14, 15-H), 0.88 (3H, dd, J 7.3 and 6.0, 3' or 5'-H), 0.87 (3H, t, J 7.4, 3' or 5'-H); δ_C (90 MHz, $CDCl_3$) 158.3 (5-C), 140.9 (10-C), 136.1 (7-C), 129.1 (9, 11-C), 128.4 (8, 12-C), 113.6 (6-C), 81.0 (1'-C), 69.5 (2''-C), 59.2 (1-C), 55.1 (5''-C), 50.4 (7'-C), 39.6 (1'-C), 38.9 (3'' or 4''-C), 28.1 (14, 15-C), 27.2 (2 or 3-C), 26.7 (2 or 3-C), 25.1 (3'' or 4''-C), 24.6 (2', 4'-C), 9.1 (3' or 5'-C), 8.7 (3' or 5'-C); $[\alpha]_D^{20}$ –45.7 (*c* 1.29, $CHCl_3$).

(2''*S*)-[1-(4, 4-Dimethyl-5-p-tolyl-hex-5-enyl)pyrrolidin-2''-yl]-diphenylmethanol (290).



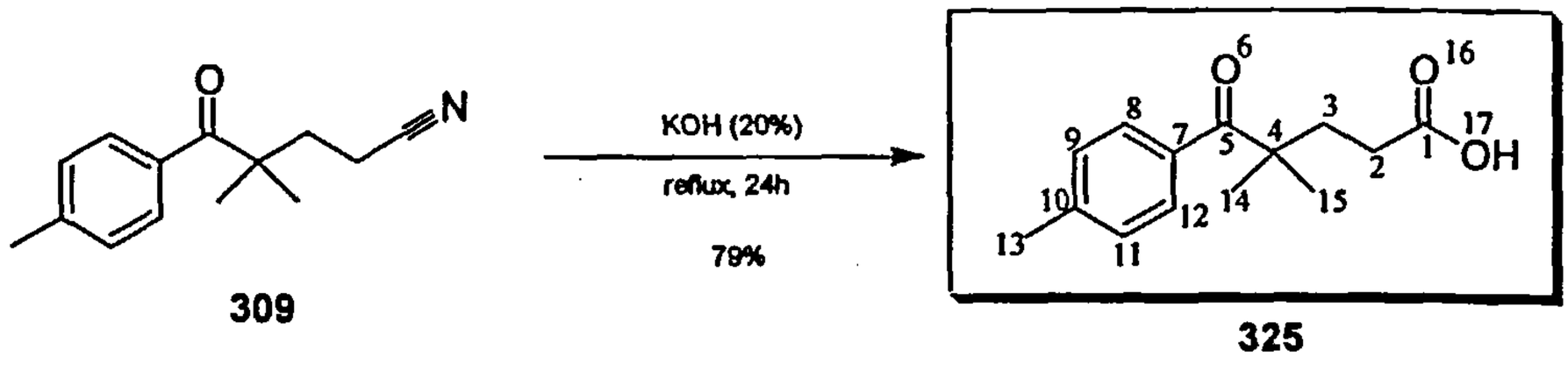
243 **290**

Table 3

To a solution of 6-bromo2-*p*-tolyl-hex-1-ene **243** (468 mg, 1.67 mmol) in acetonitrile (10 mL) was sequentially added diphenyl-L-prolinol **317** (0.55 g, 2.17 mmol) and anhydrous potassium carbonate (2.3 g, 16.65 mmol). The resulting suspension was refluxed for 4 days. The mixture was then diluted with ethyl acetate, filtered and concentrated in *vacuo* to give an oil. The crude product was purified by flash column chromatography (diethyl ether/ hexane 1:4) to yield amino styrene **290** as a low melting solid (0.467 g, 76%); R_f 0.3 (diethyl ether/ hexane 1:4); ν_{max} (neat)/cm^{-1} 3328 (bs), 3084 (m), 2924 (s), 2855 (s), 2807 (m), 2360 (w), 1811 (w), 1619 (w), 1512 (m), 1450 (s), 1378 (s), 1033 (m), 906 (w), 827 (s), 752 (s); δ_H (360 MHz, $CDCl_3$) 7.57-7.51 (4H, m, 3', 7', 9', 13'-H), 7.26 (1H, t, J 7.7, 5' or 11'-H), 7.19 (1H, t, J 7.5, 5' or 11'-H), 7.14-7.10 (4H, m, 4', 6', 10', 12'-H), 7.08 (2H, d, J 7.8, 8, 12-H), 6.92 (2H, d, J 7.9, 9, 11-H), 5.01 (1H, d, J 1.6, 6-H_b), 4.80 (1H, d, J 1.6, 6-H_a), 3.75 (1H, dd, J 9.1 and 4.0, 2''-H), 3.19-3.16 (1H, m, 5''-H_a or H_b), 2.35 (3H, s, 13-H), 2.33-2.28 (1H, m, 5''-H_a or H_b), 2.21-1.97 (1H, m, 1-H_a or H_b), 1.91-1.60 (5H, m, 1-H_a or H_b, 3'', 4''-H), 1.26-1.14 (2 or 3-H), 0.98 (6H, s, 14, 15-H), 0.95-0.79 (2 or 3-H); δ_C (90 MHz, $CDCl_3$) 158.0 (5-

C), 148.6 (2' or 8'-C), 147.1 (2' or 8'-C), 140.9 (10-C), 136.2 (7-C), 129.1 (9, 11-C), 128.4 (8, 12-C), 128.3 (4', 6', 10', 12'-H), 126.5 (5', 11'-C), 126.0 (3', 7', 9', 13'-H), 113.7 (6-C), 78.2 (1'-C), 71.6 (2''-C), 57.1 (1-C), 55.7 (5''-C), 39.3 (4-C), 38.5 (2 or 3-C), 30.0 (3''-C), 28.3 (14 or 15-C), 28.2 (14 or 15-C), 24.9 (4''-C), 24.4 (2 or 3-C), 21.6 (13-C); m/z (FAB) 455 ($[M+2H]^+$; 11), 453 (M^+; 10), 270 (100), 183 (2), 200 (8), 119 (65), 105 (95); HRMS m/z (FAB) calculated for $C_{32}H_{41}NO$ $[(M+2H)^+]$, 455.3180, found 455.3188; $[\alpha]_D^{20}$ 28.9 (*c* 1.39, $CHCl_3$).

4, 4-Dimethyl-5-oxo-5-*p*-tolyl-pentanoic acid (325).

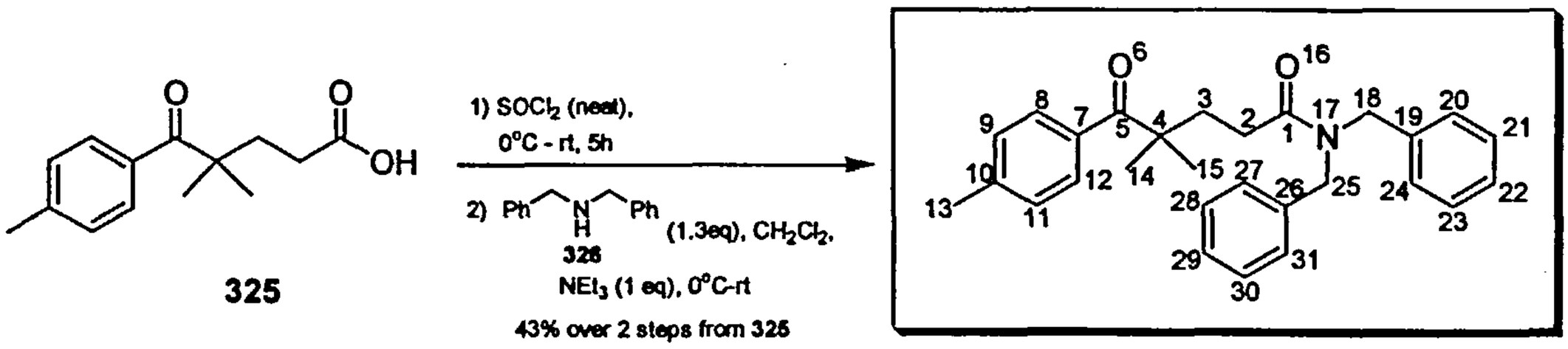


Scheme 100

In a one neck 50 mL round bottom flask containing keto-nitrile **309** (2.7 g, 12.6 mmol) was added aqueous potassium hydroxide (20 mL, 20%) at 0°C. The resulting cloudy mixture was then refluxed for 24 hours. Once the reaction was complete by tlc, the mixture was extracted with diethyl ether (20 mL x 2), acidified with hydrochloric acid and extracted again with diethyl ether (20 mL x 3). The combined ethereal extracts were dried over anhydrous magnesium sulphate and concentrated to give a colourless oil which solidified upon standing. The resulting solid was recrystalised from hexane/

toluene (1:1) to afford white needle like crystals upon standing (2.33 g, 79%); R_f 0.27 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 2924 (s), 1788 (w), 1699 (s), 1665 (s), 1607 (m), 1461 (s), 1377 (m), 1304 (s), 1235 (m), 963 (m), 836 (m); δ_H (360 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.2, 8, 12-H), 7.20 (2H, d, *J* 8.2, 9, 11-H), 2.38 (3H, s, 13-H), 2.33-2.28 (2H, m, 2-H), 2.12-2.08 (2H, m, 3-H), 1.35 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$), 207.6 (5-C), 179.9 (1-C), 142.3 (10-C), 135.7 (7-C), 129.3 (9, 11-C), 128.5 (8, 12-C), 47.3 (4-C), 35.8 (3 or 2-C), 30.2 (2 or 3-C), 26.5 (14, 15-C), 21.9 (13-C); *m/z* (FAB) 235 ($[M+H]^+$; 10), 218 (5), 217 (41), 203 (3), 189 (18), 165 (8), 159 (7), 145 (6), 133 (9), 123 (7), 119 (100), 115 (9), 109 (7), 105 (15); HRMS *m/z* (FAB) calculated for $C_{14}H_{19}O_3$, 235.1334 ($[M+H]^+$), found 235.1340

4, 4-Dimethyl-5-oxo-5-*p*-tolyl-pentanoic acid dibenzylamide (327).

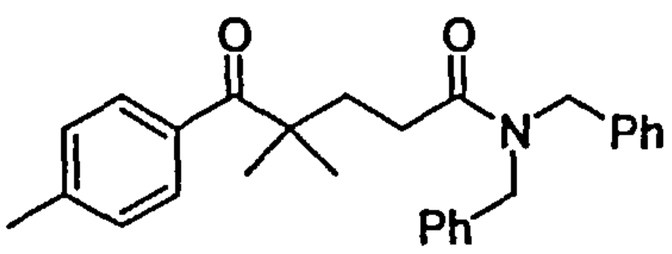


Scheme 101

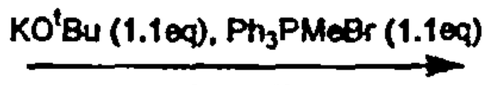
To 4, 4-Dimethyl-5-oxo-5-*p*-tolyl-pentanoic acid **325** (1.86 g, 7.95 mmol) at 0°C and under an argon atmosphere was added thionyl chloride (10 mL, 137 mmol). The ice bath was then removed and the mixture left to stir at room temperature for 5 hours. Excess thionyl chloride was removed in vacuo and the crude acid chloride was transferred to a two neck round bottom flask under an argon atmosphere. To the

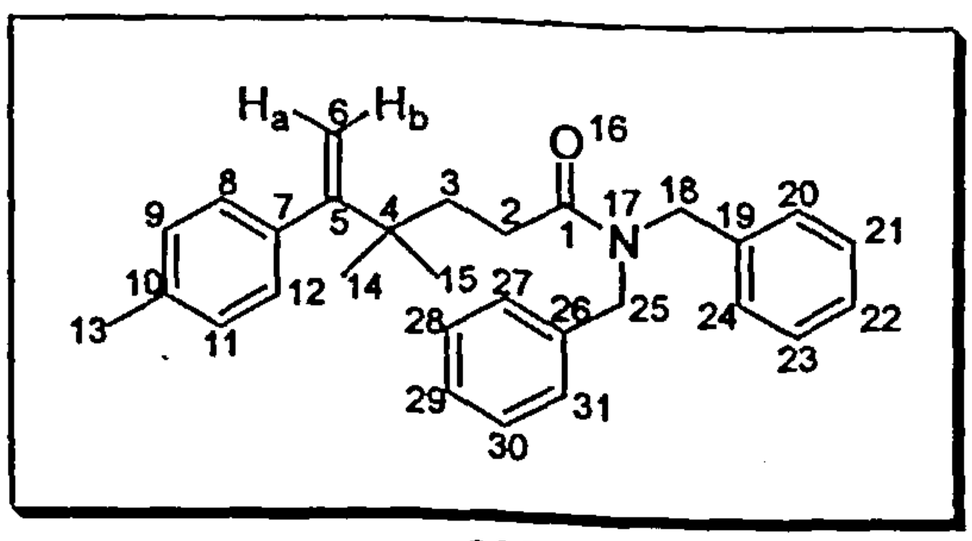
resulting yellow oil was added dichloromethane (10 mL) and the solution cooled to 0°C. To the solution was sequentially added triethylamine (1.13 mL, 8.12 mmol) and dibenzylamine (2.04 mL, 10.6 mmol) dropwise and the reaction was left to stir for 18 hours at room temperature. The mixture was then washed with hydrochloric acid (1M, 20 mL x2) and saturated sodium chloride. The organic layer was dried over anhydrous magnesium sulphate and concentrated in vacuo to yield a dark brown oil, which was purified by flash column chromatography (diethyl ether/ hexane 1:1) to give the amide **327** as a yellow oil (1.43 g, 43% over 2 steps); R_f 0.3 (diethyl ether/ hexane 1:1.5); ν_{max} (neat)/cm^{-1} 3063 (w), 3030 (m), 2970 (s), 2927 (s), 2427 (w), 2361 (w), 2245 (w), 1788 (w), 1648 (s), 1607 (s), 1432 (s), 1364 (s), 1214 (s), 1081 (m), 1029 (m), 962 (m); δ_H (360 MHz, $CDCl_3$) 7.59 (2H, d, *J* 8.1, 8, 12-H), 7.39-7.21 (6H, m, 20, 24, 27, 31-H and 21, 23-H or 28, 30-H), 7.19-7.13 (2H, m, 21, 23-H or 28, 30-H), 7.14 (2H, d, *J* 8.1, 9, 11-H), 7.04 (2H, d, *J* 6.6, 22, 29-H), 4.56 (2H, s, 18 or 25-H), 4.33 (2H, s, 18 or 25-H), 2.36 (3H, s, 13-H), 2.34-2.31 (2H, m, 2-H), 2.24-2.19 (2H, m, 3-H), 1.32 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 209.5 (5-C), 175.3 (1-C), 143.9 (10-C), 139.4 (19 or 26-C), 138.5 (19 or 26-C), 137.4 (7-C), 130.9 (9, 11-C), 130.6 (8, 12-C), 130.3 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 130.2 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 129.6 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 129.4 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 128.4 (22, 29-C), 51.9 (18 or 25-C), 50.2 (18 or 25-C), 49.2 (4-C), 38.7 (3-C), 31.1 (2-C), 28.3 (14, 15-C), 23.5 (13-C); *m/z* (FAB) 414 ($[M+H]^+$; 51), 294 (10), 281 (4), 252 (7), 239 (3), 216 (39), 207 (8), 198 (68), 179 (9), 164 (28), 145 (13), 133 (19), 119 (100); HRMS *m/z* (FAB) calculated for $C_{28}H_{32}NO_2$, 414.2433 ($[M+H]^+$), found 414.2440.

4, 4-Dimethyl-5-p-tolyl-hex-5-enoic acid dibenzylamide (328).



327





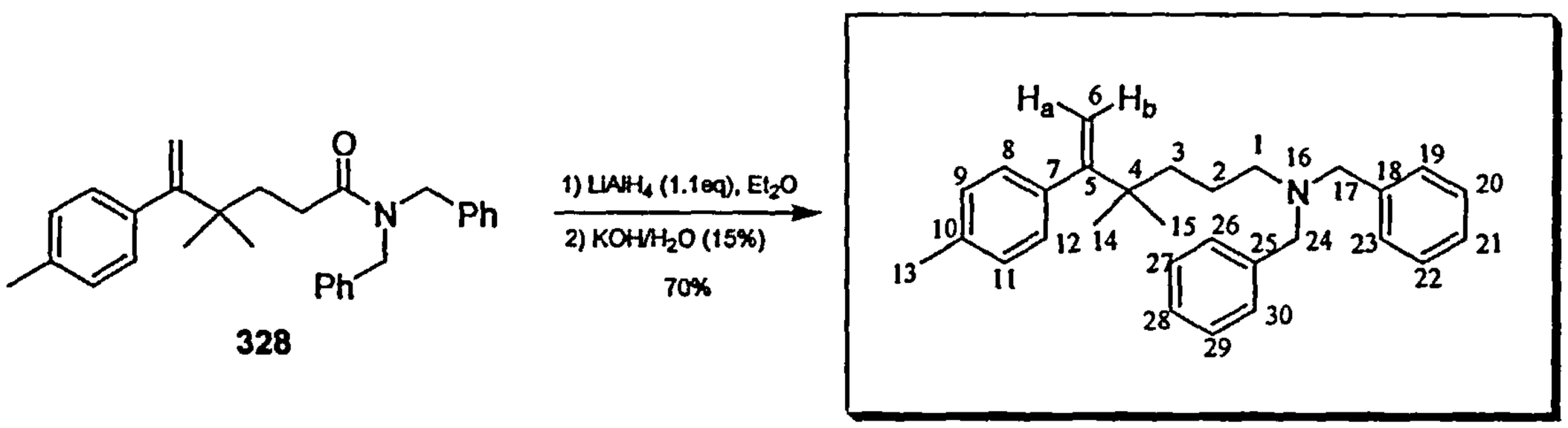
328

Scheme 102

Potassium *tert*-butoxide (0.43 g, 3.81 mmol), methyltriphenylphosphonium bromide (1.36 g, 3.81 mmol) and toluene (20 mL) were placed in a 100 mL two neck round bottom flask, fitted with a condenser and under an argon atmosphere. The mixture was refluxed with stirring for 1.5 hours at which point it became bright yellow. To this was added a solution of 4, 4-Dimethyl-5-oxo-5-*p*-tolyl-pentanoic acid dibenzylamide **327** (1.43 g, 3.46 mmol) in toluene (10 mL) dropwise at ~35°C. The resulting orange mixture was then refluxed for a further 4 hours and then left to stir overnight at room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and water (10 mL), stirred for a further 5 minutes and the organic layer was separated from the aqueous. The aqueous layer was washed with diethyl ether (10 mL x2) and the combined organic layers were rotary evaporated to give a yellow oil. The crude product was purified by flash column chromatography (diethyl ether/hexane 1:4) to afford the title compound **328** as a colourless oil (0.92 g, 65% or 73% based on recovery); R_f 0.35 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 2087 (w), 3059 (w), 3027 (m), 2976 (m), 2919 (m), 2868 (m), 2362 (w), 1833 (w), 1644 (s), 1604 (s), 1495 (s), 1433 (s), 1211 (m), 1083 (m), 915 (m); δ_H (360 MHz, $CDCl_3$) 7.39 (6H, m, 21, 22, 23-H and 28, 29,

30-H), 7.19 (2H, d, *J* 6.5, 20, 24-H or 27, 31-H), 7.13 (2H, d, *J* 7.1, 20, 24-H or 27, 31-H), 7.01 (2H, d, *J* 7.9, 8, 12-H), 6.93 (2H, d, *J* 8.0, 9, 11-H), 5.06 (1H, d, *J* 1.5, 6-H_a), 4.82 (1H, d, *J* 1.5, 6-H_b), 4.59 (2H, s, 18 or 25H), 4.37 (2H, s, 18 or 25-H), 2.43-2.38 (2H, m, 2-H), 2.31 (3H, s, 13-H), 1.84-1.79 (2H, m, 3H), 1.09 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 174.2 (1-C), 157.2 (5-C), 140.3 (10-C), 137.8 (19 or 26-C), 137.0 (19 or 26-C), 129.2 (9, 11 or 8, 12-C), 128.8 (9, 11 or 8, 12-C), 128.7 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 128.5 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 127.8 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 127.6 (20, 24 or 27, 31 or 21, 23 or 28, 30-C), 126.7 (22, 29-C), 114.3 (6-C), 50.3 (18 or 25-C), 48.5 (18 or 25-C), 39.2 (4-C), 36.5 (3-C), 29.4 (2-C), 28.2 (14, 15-C), 21.3 (13-C); *m/z* ($[M+H]^+$); 100), 338 (3), 320 (3), 294 (11), 252 (6), 230 (3), 204 (3), 195 (15), 180 (11), 164 (18), 140 (14), 132 (11), 119 (48); HRMS *m/z* (FAB) calculated for $C_{29}H_{34}NO$, 412.2640 ($[M+H]^+$), found 412.2647.

Dibenzyl-(4, 4-dimethyl-5-p-tolyl-hex-5-enyl)amine (291).

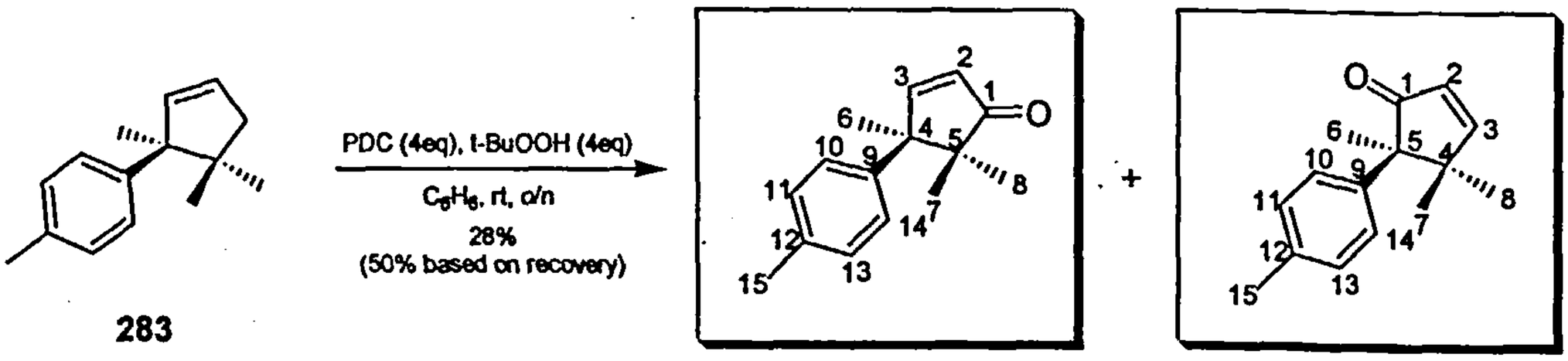


Scheme 102

To a flame dried two neck round bottom flask under an argon atmosphere was added $LiAlH_4$ (10.2 mg, 0.27 mmol) and dry diethyl ether (1 mL). The suspension was then

cooled to 0°C and 4, 4-Dimethyl-5-p-tolyl-hex-5-enoic acid dibenzylamide **328** dissolved in diethyl ether (2 mL) was added. The ice bath was removed and the reaction was stirred at room temperature overnight. The reaction was then cooled again to 0°C and aqueous potassium hydroxide (15%) was carefully added dropwise. The aqueous layer was extracted with diethyl ether (10 mL x 3) and the combined organics were washed with saturated sodium chloride. After drying over magnesium sulphate the organic portion was concentrated under reduced pressure to give the crude amine **291** as a colourless oil. The residue was purified by flash column chromatography (diethyl ether/ hexane 1:3) to afford **291** as a colourless oil (67.7 mg, 70%); R_f 0.3 (diethyl ether/ hexane 1:1); ν_{max} (neat)/cm^{-1} 3085 (w), 3026 (w), 2947 (m), 2793 (m), 2427 (w), 2360 (w), 1788 (w), 1726 (w), 1452 (s), 1125 (w), 1028 (m), 904 (m), 824 (m); δ_H (360 MHz, $CDCl_3$) 7.36-7.14 (10H, m, 19, 23, 26, 30, 20, 22, 27, 29, 21, 28-H), 7.00 (2H, d, *J* 7.9, 9, 11-H), 6.94 (2H, d, *J* 8.0, 8, 12-H), 5.08 (1H, d, *J* 1.7, 6-H_b), 4.82 (1H, d, *J* 1.6, 6-H_a), 3.54 (4H, s, 17, 24-H), 2.34 (2H, q, *J* 5.6, 1-H), 2.31 (3H, s, 13-H), 1.55-1.44 (2H, m, 2-H), 1.27-1.22 (2H, m, 3-H), 1.05 (6H, s, 14, 15-H); δ_C (90 MHz, $CDCl_3$) 158.2 (5-C), 140.8 (10 or 7-C), 140.4 (18, 25-C), 136.2 (7 or 10-C), 129.2 (19, 23 and 26, 30-C), 129.1 (9, 11-C), 128.5 (20, 22 and 27, 29-C), 128.5 (9, 11-C), 127.1 (21, 28-C), 113.7 (6-C), 58.7 (17, 24-C), 54.3 (1-C), 39.5 (4-C), 38.7 (3-C), 28.1 (14, 15-C), 22.5 (2-C), 21.5 (13-C); *m/z* (FAB) 398 ($[M+H]^+$; 41), 397 (M^+; 8), 396 (54), 320 (12), 306 (6), 237 (18), 236 (100), 211 (13), 210 (79), 194 (4), 180 (9), 158 (8), 145 (8), 131 (9), 119 (13); HRMS m/z (FAB) calculated for $C_{29}H_{36}N$, 398.2848 ($[M+H]^+$), found 398.2840.

(4*SR*)-4, 5, 5-Trimethyl-4-*p*-tolyl-cyclopent-2-enone (329) and (5*SR*)-4, 4, 5-trimethyl-5-*p*-tolyl-cyclopent-2-enone (330).



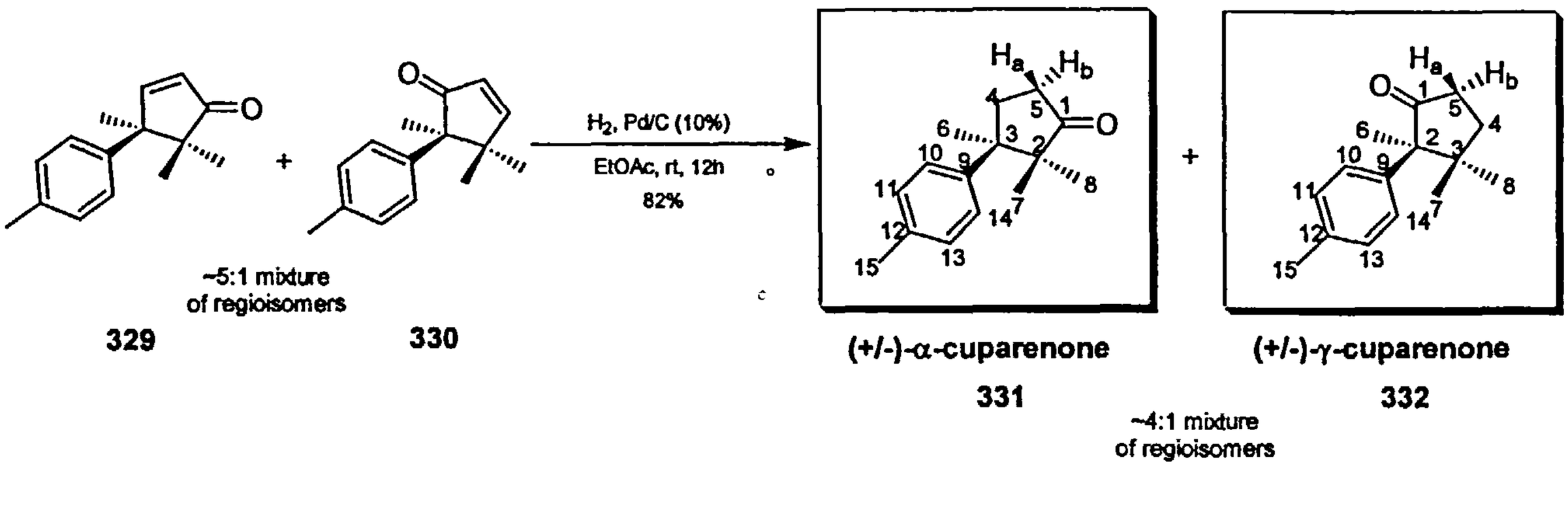
Scheme 103

To a stirred solution of 1-methyl-4-(1, 5, 5-trimethyl-cyclopent-2-enyl)benzene **283** (28.5 mg, 0.14 mmol) in benzene (1.7 mL) and Celite (0.16 g) at 5°C was added pyridinium dichromate (PDC) (0.19 mg, 0.56 mmol) followed by the addition of *tert*-butyl hydroperoxide (5M, 112 μL, 0.56 mmol). After 15 minutes at 5°C, the resulting cloudy mixture was then left to stir at room temperature overnight. Diethyl ether (10 mL) was then added and the reaction was filtered through a pad of Celite and washed twice with diethyl ether (2 x 10 mL). The combined filtrates were rotary evaporated to a yellow oil, which was purified by flash column chromatography (diethyl ether/ hexane 1:19) to afford a 5:1 colourless mixture of regioisomers **329** and **330** (8.5 mg, 28% or 50% based on recovery of **283**).

^{1}H-NMR for 4SR-(**329**): δ_H (360 MHz, $CDCl_3$) 7.75 (1H, d, *J* 5.9, 3-H), 7.14 (2H, d, *J* 8.2, 10, 14-H), 7.07 (2H, d, *J* 8.4, 11, 13-H), 6.22 (1H, d, *J* 5.9, 2-H), 2.34 (3H, s, 15-H), 1.45 (3H, s, 7 or 8-H), 1.19 (3H, s, 7 or 8-H), 0.53 (3H, s, 6-H). Analytical data agree with that reported in the literature.[21, 32]

^{1}H-NMR for 5SR-(**330**): δ_H (360 MHz, $CDCl_3$) 7.43 (1H, d, *J* 5.8, 3-H), 7.14 (2H, d, *J* 8.2, 10, 14-H), 7.07 (2H, d, *J* 8.4, 11, 13-H), 6.16 (1H, d, *J* 5.8, 2-H), 2.31 (3H, s, 15-H), 1.43 (3H, s, 7 or 8-H), 1.21 (3H, s, 7 or 8-H), 0.66 (3H, s, 6-H).

α-Cupaenone (331) and γ-cuparenone (332).



Scheme 104

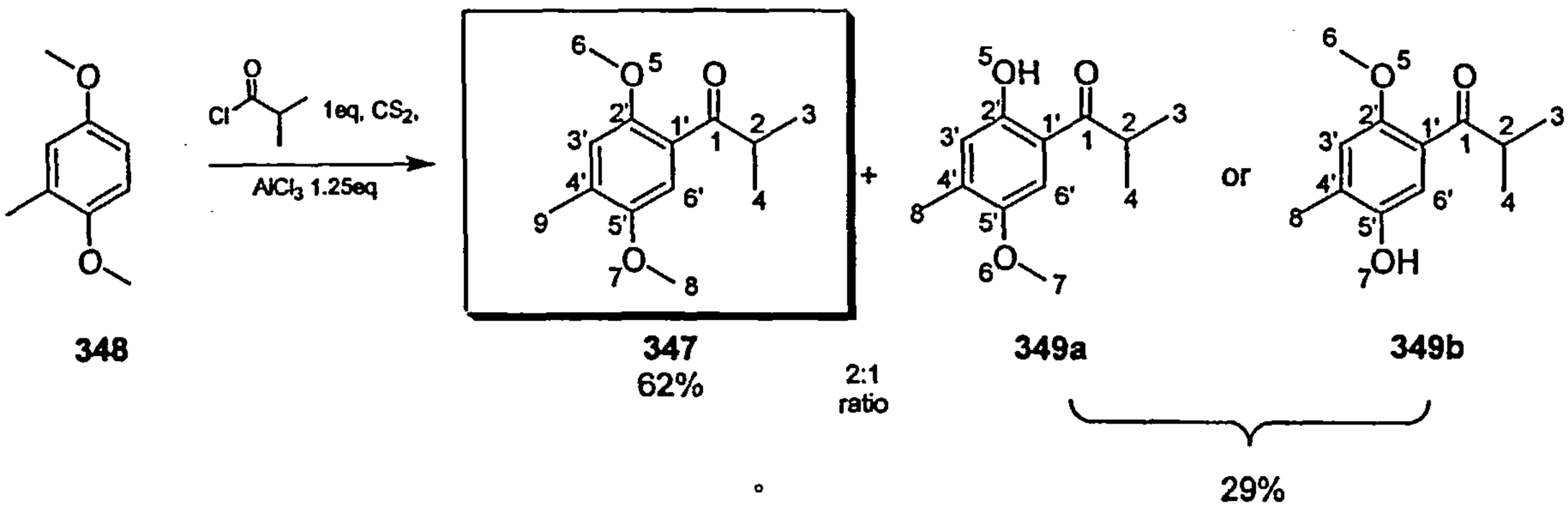
To a 5:1 regioisomeric mixture of **329** and **330** (8.5 mg, 0.03 mmol) in EtOAc was added 10% Pd on charcoal (10 mg). The mixture was stirred under atmospheric hydrogen at room temperature for 12 hours. After the reaction had gone to completion by t.l.c, the catalyst was removed by filtration through celite and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The resulting pale yellow oil was purified by column chromatography to afford a 4:1 mixture of regioisomers **331** and **332**.

α-Cuparenone (**331**): δ_H (360 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.3, 10, 14-H), 7.16 (2H, d, *J* 8.2, 11, 13-H), 2.54-2.48 (1H, m, 5-H_a or H_b), 2.47-2.40 (2H, m, 4-H), 2.34 (3H, s, 15-

H), 1.95-1.88 (1H, m, 5-H_a or H_b), 1.26 (3H, s, 7 or 8-H), 1.17 (3H, s, 7 or 8-H), 0.61 (3H, s, 6-H). Analytical data agree with that reported in the literature.[21, 32]

γ-Cuparenone (**332**): δ_H (360 MHz, $CDCl_3$) 7.09 (2H, d, *J* 8.2, 10, 14-H), 7.02 (2H, d, *J* 8.3, 11, 13-H), 2.72-2.54 (2H, m, 4-H), 2.40-2.37 (1H, m, 5-H_a or H_b), 2.31 (3H, s, 15-H), 1.87-1.77 (1H, m, 5-H_a or H_b), 1.32 (3H, s, 7 or 8-H), 1.06 (3H, s, 7 or 8-H), 0.67 (3H, s, 6-H)

1-(2', 5'-Dimethoxy-4'-methyl-phenyl)-2-methyl-propan-1-one (347) and 1-(2'-hydroxy, 5'-methoxy-4'-methyl-phenyl)-2-methyl-propan-1-one (349)



Scheme 108

To a solution of 2,5-dimethoxytoluene (10 g, 65.7 mmol) and isobutyrylchloride (7.57 mL, 72.3 mmol) in CS_2 (85 mL) was added portionwise $AlCl_3$ (10.95 g, 82.1 mmol) at such a rate to maintain the temperature of the reaction below 10°C. The reaction mixture was then stirred at room temperature overnight. The resulting dark green reaction mixture was decomposed by pouring into ice and dilute HCl (80 mL, 0.5M). The organic phase was separated from the aqueous and the aqueous was extracted with dichloromethane (50 mL x 3). The combined organic extracts were dried over $MgSO_4$ and rotary evaporated to give the crude product as a yellow oil (14.3 g, 98%) in a 2:1 ratio of products. The crude product was purified by column chromatography (hexane/diethyl ether 4:1) to afford two products **347** (9.1 g, 62%) and **349** (4 g, 29%) as pale yellow solids.

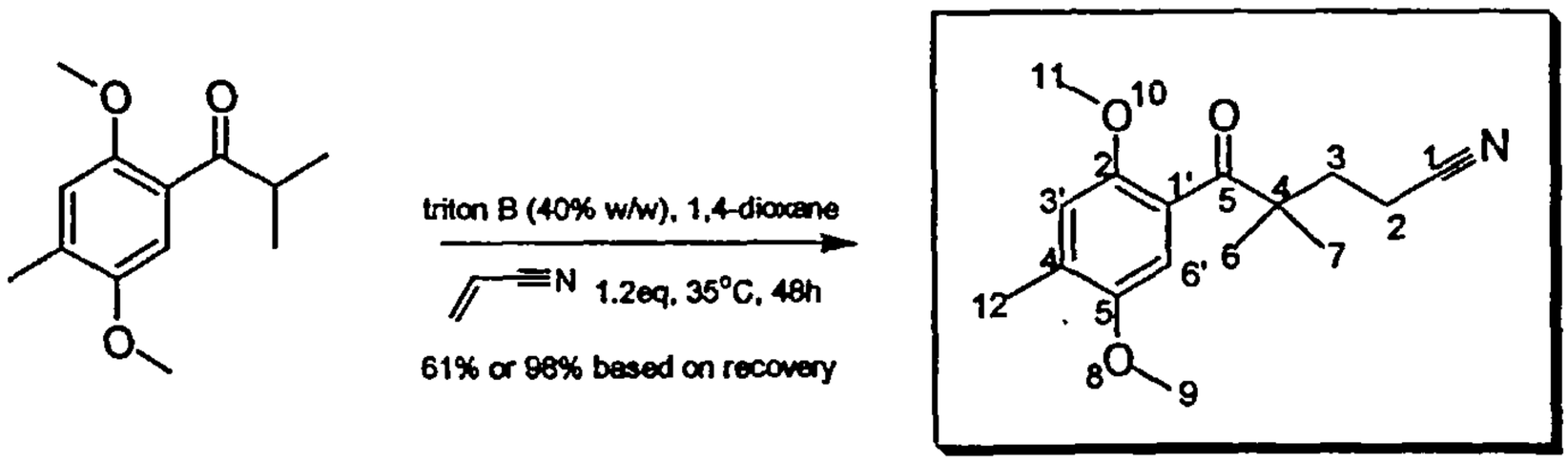
Major: 1-(2', 5'-Dimethoxy-4'-methyl-phenyl)-2-methyl-propan-1-one (**347**).

R_f 0.64 (hexane/diethyl ether 1:1); ν_{max} (nujol/cm^{-1}) 1652 (m), 1610 (m), 1499 (s), 1464 (s), 1396 (s), 1217 (s), 1045 (s); δ_H (360 MHz, $CDCl_3$) 7.13 (1H, s, 6'-H), 6.77 (1H, s, 3'-H), 3.85 (3H, s, 6 or 8-H), 3.81 (3H, s, 6 or 8-H), 3.62-3.54 (1H, m, 2-H), 2.25 (3H, s, 9-H), 1.15 (3H, s, 3 or 4-H), 1.13 (3H, s, 3 or 4-H); δ_C (90 MHz, $CDCl_3$) 207.3 (1-C), 152.7 (2' or 5'-C), 152.1 (2' or 5'-C), 132.9 (1' or 4'-C), 126.1 (1' or 4'-C), 115.1 (3' or 6'-C), 111.8 (3' or 6'-C), 56.5 (6 or 8-C), 56.2 (6 or 8-C), 40.3 (2-C), 19.2 (3 or 4-C), 17.1 (3 or 4-C); Analytical data agree with that reported in the literature.[151]

Minor: 1-(2'-hydroxy, 5'-methoxy-3'-methyl-phenyl)-2-methyl-propan-1-one (349).

R_f 0.64 (hexane/diethyl ether 1:1); ν_{max} (nujol/cm^{-1}) 1641 (m), 1620 (m), 1503 (m), 1466 (m), 1204 (m), 1137 (m), 1033 (w); For compound (**349a**) δ_H (360 MHz, $CDCl_3$) 7.07 (1H, s, 6'-H), 6.80 (1H, s, 3'-H), 3.82 (3H, s, 7-H), 3.58-3.50 (1H, m, 2-H), 2.24 (3H, s, 8-H), 1.27 (3H, s, 3 or 4-H), 1.25 (3H, s, 3 or 4-H); δ (90 MHz, $CDCl_3$) 210 (1'-C), 158.2 (5'-C), 150.7 (2'-C), 138.6 (1'-C), 120.8 (6'-C), 115.7 (4'-C), 109.3 (3'-C), 56.3 (7-C), 35.3 (2-C), 19.7 (3 or 4-C), 17.3 (8-C); For compound (**349b**) δ_H (360 MHz, $CDCl_3$) 7.07 (1H, s, 6'-H), 6.80 (1H, s, 3'-H), 3.82 (3H, s, 6-H), 3.58-3.50 (1H, m, 2-H), 2.24 (3H, s, 8-H), 1.27 (3H, s, 3 or 4-H), 1.25 (3H, s, 3 or 4-H); δ (90 MHz, $CDCl_3$) 210 (1'-C), 158.2 (2'-C), 150.7 (5'-C), 138.6 (1'-C), 120.8 (6'-C), 115.7 (4'-C), 109.3 (3'-C), 56.3 (7-C), 35.3 (2-C), 19.7 (3 or 4-C), 17.3 (8-C).

5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-5-oxo-pentanenitrile (346).



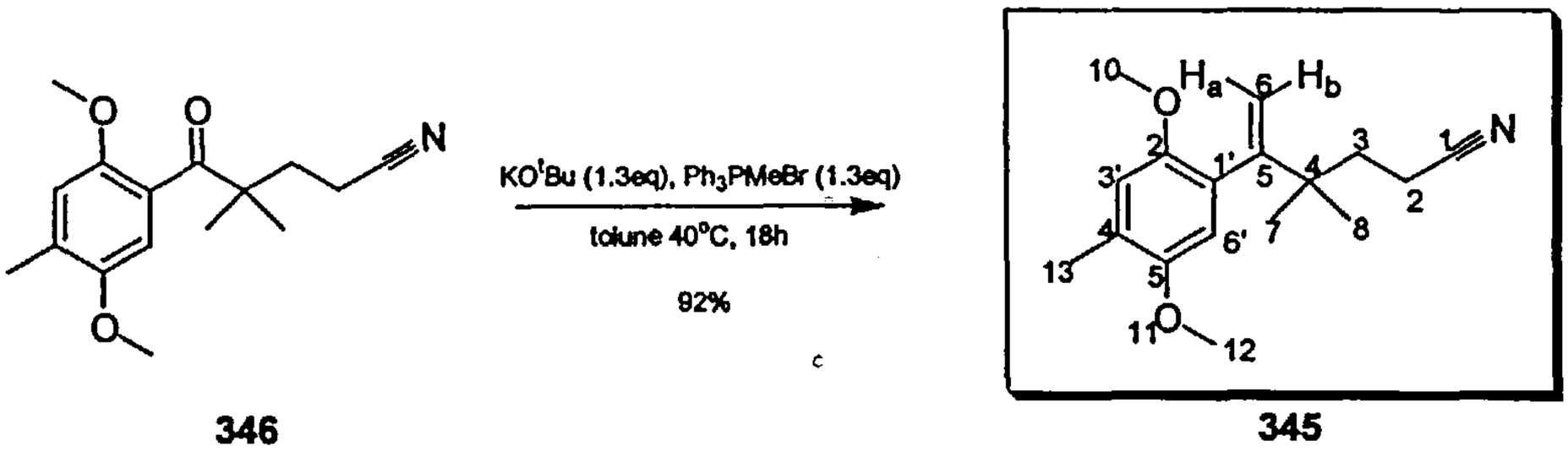
347 346

Scheme 109

To a stirred mixture of 1-(2', 5'-Dimethoxy-4'-methyl-phenyl)-2-methyl-propan-1-one **347** (2.69 g, 12.1 mmol), dioxane (1.97 mL, 23.11 mmol) and benzyltrimethylammonium hydroxide (40% w/w, 0.55 mL, 1.21 mmol) was added via syringe acrylonitrile (0.96 mL, 14.52 mmol) dropwise over 2 minutes. The reaction mixture was heated to 30-35°C and maintained at that temperature for 48 hours. The resulting dark brown/orange solution was then acidified using hydrochloric acid (10%) and extracted with dichloromethane (50 mL x 3). The combined organic extract were freed from dioxane by washing with water (x3) and then dried over magnesium sulphate. The organics were filtered and concentrated under reduced pressure to give the crude product as a brown oil. The residue was purified by column chromatography (hexane/diethyl ether 4:1) to afford the title compound **346** as a pale yellow solid (2.01 g, 61% or 96% based on recovery); R_f 0.1 (hexane/diethyl ether 4:1); δ_H (360 MHz, $CDCl_3$) 6.73 (1H, s, 6'-H), 6.47 (1H, s, 3'-H), 3.77 (6H, s, 9, 11-H), 2.37-2.42 (2H, m, 2-H), 2.23 (3H, s, 12-H), 2.00-2.06 (2H, m, 3-H), 1.23 (6H, s, 6, 7-H); δ_C (90 MHz, $CDCl_3$) 212.3 (5-C), 151.9 (2' or 5'-C), 149.2 (2' or 5'-C), 129.5 (4'-C), 128.0 (1'-C), 120.7 (1-C), 114.7 (6'-C), 109.2 (3'-C), 56.4 (9, 11-C), 48.1 (4-C), 35.5 (2-C), 25.1 (6,

7-C), 16.9 (3-C), 13.5 (12-C); *m/z* (FAB) 276 ($[M+H]^+$; 56), 275 (M^+; 32), 178 (100), 164 (12), 151 (11); HRMS m/z (FAB) calculated for $C_{16}H_{22}NO_3$, 276.1600 ($[M+H]^+$), found 276.1592.

5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-hex-5-enenitrile (345).

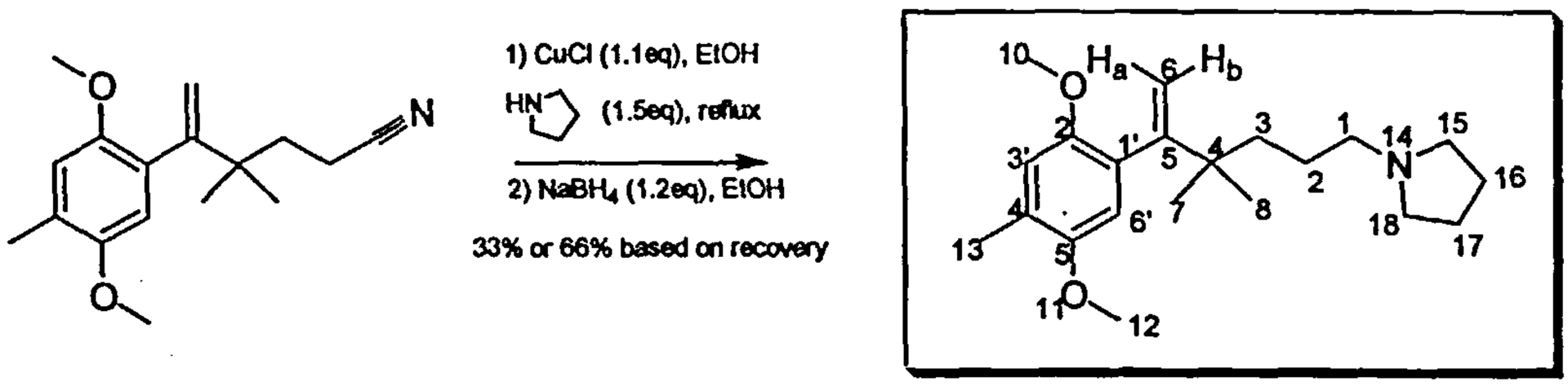


Scheme 110

Potassium *tert*-butoxide (0.53 g, 4.73 mmol), methyltriphenylphosphonium bromide (1.69 g, 4.73 mmol) and toluene (30 mL) were placed in a 100 mL two neck round bottom flask, fitted with a condenser and under an argon atmosphere. The reaction mixture was refluxed for 2 hours at which point it became bright yellow. The reaction mixture was then cooled to ~60°C and 5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-5-oxo-pentanenitrile **346** (1 g, 3.64 mmol) dissolved in toluene (5 mL) was added dropwise over a period of 10 minutes. The resulting orange mixture was then stirred at 40°C for 18 hours. The reaction mixture was diluted with diethyl ether (20 mL) and water (10 mL), stirred for a further 5 minutes and the organic layer was separated from the aqueous. The aqueous layer was extracted with diethyl ether (10 mL x 2) and the combined organic layers were dried over magnesium sulphate and rotary

evaporated to give a yellow oil. The crude product was purified by flash column chromatography (hexane/diethyl ether 4:1) to afford the title compound **345** as a colourless oil (0.92 g, 92%); R_f 0.39 (hexane/diethyl ether 4:1); ν_{max} (nujol/cm^{-1}) 2243 (m), 1838 (w), 1737 (m), 1629 (m), 1504 (s), 1461 (s), 1212 (s), 1044 (s), 917 (m); δ_H (360 MHz, $CDCl_3$) 6.72 (1H, s, 6'-H), 5.24 (1H, d, J 1.28, 6-H_a), 4.99 (1H, d, J 1.25, 6-H_b), 3.79 (3H, s, 10 or 12-H), 3.76 (3H, s, 10 or 12-H), 3.72-2.43 (2H, m, 2-H), 2.25 (3H, s, 13-H), 1.76 (2H, t, J 5.8, 3-H), 1.11 (6H, s, 7, 8-H); δ_C (90 MHz, $CDCl_3$) 152.8 (5-C), 151.3 (2'or 5'-C), 150.5 (2' or 5'-C), 128.9 (4'-C), 126.6 (1'-C), 121.5 (1-C), 115.9 (6-C), 114.6 (3' or 6'-C), 114.3 (3' or 6'-C), 56.4 (10, 11-C), 39.6 (4-C), 37.0 (2-C), 27.7 (7, 8-C), 16.6 (13-C), 13.4 (3-C); *m/z* (FAB) 274 ($[M+H]^+$; 45), 273 (M^+; 100), 178 (10), 164 (5), 146 (4), 122 (4); HRMS (FAB) calculated for $C_{17}H_{23}NO_2$, 273.1729 (M^+), found 273.1739.

1-[5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-hex-5-enyl]pyrrolidine (343).



345 343

Scheme 111

In an oven dried, 25 mL 2 neck round bottom flask fitted with a condenser and under an argon atmosphere was added 5-(2', 5'-Dimethoxy-4'-methyl-phenyl)-4, 4-dimethyl-hex-5-enenitrile **345** (0.8 g, 2.93 mmol), ethanol (20 mL) and copper (I) chloride (0.32 g, 3.26 mmol). To this was added a solution of pyrrolidine (366 μL, 4.4 mmol) in ethanol (5 mL). The resulting green/brown mixture was then refluxed for 24 hours. The dark brown/orange mixture was then cooled to room temperature and poured with vigorous stirring into an Erlenmeyer flask (100 mL) containing aqueous NaOH (10 mL, 30%) and diethyl ether (20 mL). The mixture was stirred vigorously for 5 minutes. The organic layer was then separated and the aqueous layer was extracted with diethyl ether (x3). The combined organic extracts were dried over magnesium sulphate and evaporated to dryness to afford the crude amidine as a brown oil (0.9 g).

The crude amidine (0.9 g) was transferred to an oven dried 25 mL two neck round bottom flask, equipped with a magnetic stirrer bar and under an argon atmosphere. To this was added ethanol (10 mL) via syringe and the reaction mixture was cooled to 0°C. Sodium borohydride (0.13 g, 3.52 mmol) was added with stirring in small portions over

a period of 10 minutes. The brown solution was then left to stir overnight at room temperature. The reaction mixture was then poured into an Erlenmeyer flask (100 mL) containing NaOH (10 mL, 30%) and diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (x3). The combined organic were dried over magnesium sulphate, filtered and rotary evaporated under reduced pressure a dark brown oil. The residue was purified by column chromatography (hexane/ diethyl ether 2:3) to afford the title compound **343** as a pale yellow oil (320 mg, 33% or 66% based on recovery); R_f 0.1 (hexane/ diethyl ether 2:3); ν_{max} (neat/cm^{-1}) 2948 (s), 2783 (m), 1627 (m, C=C), 1503 (s), 1464 (m), 1388 (m), 1211 (s), 1047 (s); δ_H (360 MHz, $CDCl_3$) 6.68 (1H, s, 6'-H), 6.46 (1H, s, 3'-H), 5.21 (1H, d, J 1.6, 6-H_a), 4.88 (1H, d, J 1.5, 6-H_b), 3.76 (3H, s, 10-H), 3.72 (3H, s, 12-H), 2.54 (4H, bs, 15, 18-H), 2.42 (2H, t, J 7.9, 1-H), 2.22 (3H, s, 13-H), 1.84-1.76 (4H, m, 16, 17-H), 1.65-1.56 (2H, m, 2-H), 1.43-1.35 (2H, m, 3-H), 1.06 (6H, s, 7, 8-H); δ_C (90 MHz, $CDCl_3$) 155.0 (5-C), 151.2 (2' or 5'-C), 150.8 (2' or 5'-C), 130.5 (4'-C), 125.8 (1'-C), 114.5 (3' or 6'-C), 114.2 (6-C), 114.0 (3' or 6'-C), 57.7 (1-C), 56.6 (10 or 12-C), 15.5 (10 or 12-C), 54.7 (15, 18-C), 39.7 (3-C), 27.8 (7, 8-C), 24.6 (2-C), 23.8 (16, 17-C), 16.6 (13-C).

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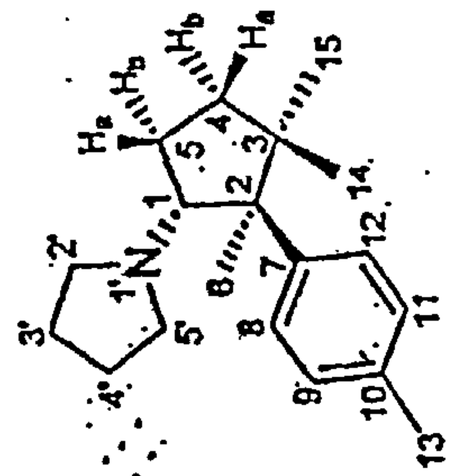
Chapter 5
Appendices

5.1 Appendix 1: NOESY spectra of major cycloadduct 281



Current Data Parameters
NAME Jul2501-5.001
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010726
Time 17.03
INSTRUM drx500
PROBHD 5 mm BBO BB-
PULPROG noesytp
TD 2048
SOLVENT CDCl3
NS 16
DS 4
SWH 4310.345 Hz
FIDRES 2.104661 Hz
AQ 0.2378180 sec
RG 161.3
DW 116.000 usec
DE 6.00 usec
TE 300.0 K
d0 0.00000300 sec
D1 1.46231699 sec
D8 0.80000001 sec
IN0 0.00011600 sec

CHANNEL f1
NUC1 1H
P1 11.75 usec
PL1 0.00 dB
SF01 500.1318690 MHz

F1 - Acquisition parameters
NDO 2
TD 256
SF01 500.1319 MHz
FIDRES 18.837284 Hz
SW 8.818 ppm

F2 - Processing parameters
SI 1024
SF 500.1300115 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.1300115 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 25.00 cm
CX1 25.00 cm
F2PLO 8.006 ppm
F2LO 4004.29 Hz
F2PHI 0.196 ppm
F2HI 98.04 Hz
F1PLO 8.006 ppm
F1LO 4004.29 Hz
F1PHI 0.196 ppm
F1HI 98.04 Hz
F2PPMCM 0.31242 ppm/cm
F2HZCM 156.25000 Hz/cm
F1PPMCM 0.31242 ppm/cm
F1HZCM 156.25000 Hz/cm

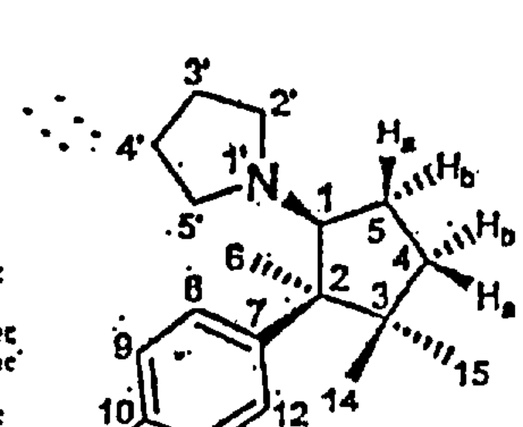
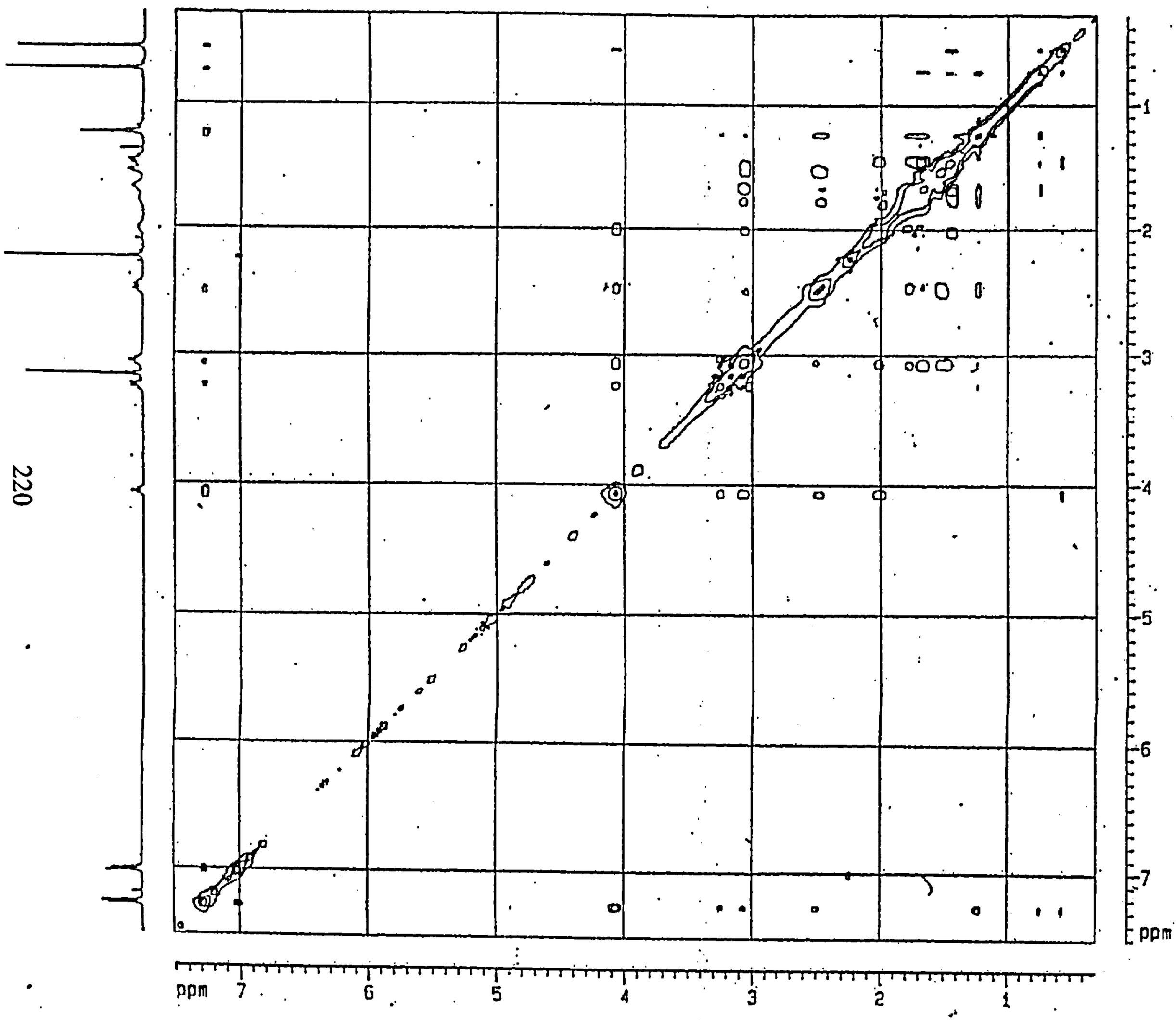


Figure 47. NOESY spectra of minor cycloadduct 28d



AGP3/
NOESYPHSW CDCl3 (C:\u) General 2

Current Data Parameters

NAME	Oct18-2001-4-2
EXPNO	8
PROCNO	1

F2 - Acquisition Parameters

Date_	20011018
Time	17.38
INSTRUM	spect
PROBHD	5 mm CHP 1H/1
PULPROG	noesyph
TD	2048
SOLVENT	CDCl3
NS	16
DS	4
SWH	3981.954 Hz
FIDRES	1.753884 Hz
AQ	0.2051318 sec
RG	40.3
DW	139.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.98600294 sec
D8	0.80000001 sec
IN0	0.00087840 sec
NOREST	0.00000600 sec
MCWRK	0.98300147 sec
STEADY	dz

CHANNEL f1

NUC1	1H
P1	9.00 usec
PL1	0.00 dB
SFO1	400.1314308 MHz

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	400.1314 MHz
FIDRES	14.031871 Hz
SW	8.977 ppm

F2 - Processing parameters

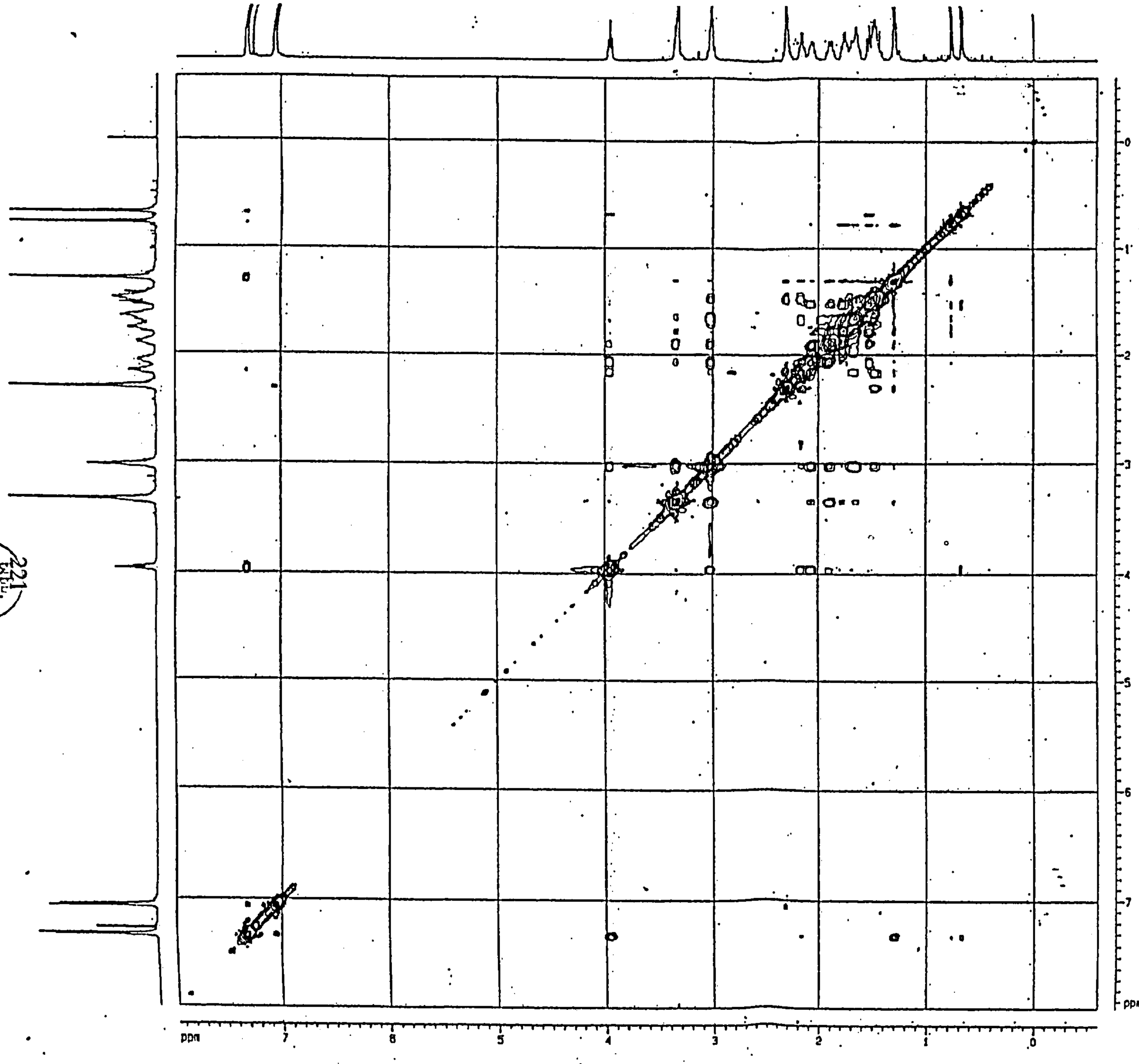
SI	1024
SF	400.1300487 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	States-TPPI
SF	400.1300487 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CY1	15.00 cm
F2PLO	7.500 ppm
F2LO	3004.48 Hz
F2PHI	0.300 ppm
F2HI	120.04 Hz
F1PLO	7.500 ppm
F1LO	3004.48 Hz
F1PHI	0.300 ppm
F1HI	120.04 Hz
F2PPMCM	0.40038 ppm/cm
F2HZCM	192.29878 Hz/cm
F1PPMCM	0.40038 ppm/cm
F1HZCM	192.29878 Hz/cm



noesytpsw_a3 CDCl3 D:/u jeh 1

Current Data Parameters

NAME	Feb0402-5.001
EXPNO	31
PROCNO	1

F2 - Acquisition Parameters

Date_	20020205
Time	0.45
INSTRUM	drx500
PROBHD	5 mm BBO BB-
PULPROG	noesytp
TD	2048
SOLVENT	CDCl3
NS	16
DS	4
SWH	4280.822 Hz
FIDRES	2.090246 Hz
AQ	0.2392564 sec
RG	32
DW	116.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
d1	1.46020602 sec
D8	0.80000001 sec
IN0	0.00011680 sec

CHANNEL f1

NUC1	1H
P1	11.75 usec
PL1	0.00 dB
SFO1	500.1318580 MHz

F1 - Acquisition parameters

NO0	2
TD	256
SFO1	500.1318 MHz
FIDRES	16.721980 Hz
SW	8.559 ppm

F2 - Processing parameters

SI	1024
SF	500.1300147 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300147 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	25.00 cm
CX1	25.00 cm
F2PLO	7.985 ppm
F2LO	3993.72 Hz
F2PHI	-0.894 ppm
F2HI	-297.10 Hz
F1PLO	7.985 ppm
F1LO	3993.72 Hz
F1PHI	-0.894 ppm
F1HI	-297.10 Hz
F2PPMCM	0.34238 ppm/cm
F2HZCM	171.23288 Hz/cm
F1PPMCM	0.34238 ppm/cm
F1HZCM	171.23288 Hz/cm